Significance of the Genomic Landscape of a De Novo Endocrine-Resistant Metastatic Hormone Receptor–Positive Breast Cancer

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ABSTRACT: Endocrine therapy with or without CDK4/6 inhibitors is the most commonly used frontline treatment option for metastatic hormone receptor–positive breast cancer. Approximately, 25% to 30% of women may have resistance to endocrine therapy, especially in the setting of certain genomic mutations in the tumor. This prompts the need to identify those patients who may benefit from frontline chemotherapy over endocrine therapy. Here, we present a case of a patient who presented with a *de novo* metastatic hormone receptor–positive breast cancer with visceral involvement (including bone marrow) as well as multiple somatic genomic alterations. The patient was treated with upfront chemotherapy, resulting in clinical and radiographic response, but rapidly progressed when she was transitioned to hormonal therapy. This report focuses on the role of upfront chemotherapy in the setting of visceral crisis including bone marrow involvement, the role of genomic alterations in contributing to endocrine resistance, and the need for biomarker-driven treatment options for hormone receptor–positive breast cancer.

KEYWORDS: Metastatic Breast cancer, visceral crisis, next generation sequencing, endocrine resistance

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Introduction

Hormone receptor–positive breast cancer comprises 75% of all malignant cancers of the breast.[1,2] Large, randomized, phase III trials have shown significant improvement in progression-free survival associated with the addition of cyclin-dependent kinase 4 and 6 (CDK4/6) inhibitors to aromatase inhibitors among hormone receptor–positive metastatic breast cancer patients in the first-line setting.[3-5] Therefore, endocrine therapy with CDK4/6 inhibitors is now the frontline treatment option for metastatic hormone receptor–positive breast cancer and has significantly improved survival outcomes, even for patients with visceral disease. However, despite the advances made in such treatment options, approximately 25% to 30% of women may have resistance (intrinsic or acquired) to endocrine therapy.[6] This prompts the need to address patients who would benefit from frontline chemotherapy over endocrine therapy, especially in the background of genomic mutations that could potentially confer intrinsic endocrine resistance in treatment-naïve *de novo* metastatic disease.

Previously, there was the notion that some patients should receive upfront chemotherapy even for hormone receptor–positive metastatic breast cancer, on the basis of the location, bulk, or aggressiveness of the disease. However, studies have examined the combination of hormonal therapy with CDK4/6 inhibitors in comparison with chemotherapy in premenopausal aggressive hormone receptor–positive breast cancer and showed better progression-free survival with hormonal therapy.[7] Nevertheless, chemotherapy has an early onset to disease response, and this may especially be important for patients with extensive tumor burden where there is an urgent need for a rapid response, such as in an impending visceral crisis.

We present a case of a patient with newly diagnosed *de novo* metastatic hormone receptor–positive breast cancer with multiple genomic alterations potentially associated with endocrine resistance. Our case report highlights the significance of next-generation sequencing (NGS) in hormone receptor-positive breast cancer and how it may provide valuable information for oncologists to make timely therapeutic decisions.

Case

We present a case of a 70-year-old postmenopausal female with a new diagnosis of metastatic breast cancer. She had initially complained of fatigue and shortness of breath, with complete blood count on arrival in the emergency room noting anemia with a Hb of 8.3 g/dL, thrombocytopenia with platelets of 122 000/μL, and abnormal liver function tests (LFTs) (AST 66 and ALT 81). A subsequent bone marrow biopsy revealed adenocarcinoma of breast origin. Imaging done at that hospital, including computed tomography (CT) chest, abdomen, and pelvis, showed bulky diffuse adenopathy in the left axilla with diffuse hepatomegaly and multiple osseous metastases in the calvarium and spine. She then underwent a biopsy of

the left axillary lymph node and liver, which showed ER (estrogen receptor) positive (Allred 8), progesterone receptor (PR) negative (Allred Score 0), and human epidermal growth factor receptor 2 (HER 2) negative adenocarcinoma of breast origin.

Patient was deemed to be in visceral crisis, given her bone marrow involvement with anemia, thrombocytopenia, and liver involvement. Unfortunately, the patient's performance status (Eastern Cooperative Oncology Group/ECOG 2) precluded her from enrollment in clinical trials. Therefore, a decision was made to initiate treatment with standard of care weekly nab-paclitaxel, which resulted in a good clinical response (improvement in platelets to 189 000/μL and normalization of LFTs) and a favorable radiographic response with a decrease in the size of her lymphadenopathy. Unfortunately, nab-paclitaxel had to be discontinued due to worsening neuropathy after 6 weekly doses. Due to the rapid hematologic improvement noted, she was started on hormonal therapy with letrozole (an aromatase inhibitor) as monotherapy. CDK 4/6 inhibitors were delayed at this time given the concern for potential worsening of cytopenia. Unfortunately, within 4 weeks of initiating letrozole, patient had a significant increase in tumor markers and an increase in hepatic transaminases consistent with progressive disease. Hence, letrozole was discontinued and patient was started on a CDK 4/6 inhibitor; abemaciclib, in addition to fulvestrant. The combination was not tolerated well due to severe diarrhea from abemaciclib requiring hospitalization, and furthermore, the tumor markers continued to increase suggesting continued disease progression. Computed tomography scan of the abdomen noted new-onset ascites apart from stable hepatic and osseous metastases. Next-generation sequencing (Omniseq Advance) was sent on the axillary lymph node biopsy specimen (obtained prior to initiation of therapy), which revealed an ERBB2 mutation S280F, RET mutation S649L, BRCA 1 copy number loss, and high tumor mutational burden (TMB) 10/Mb. Of note, our NGS panel uses an all-exon mutational profiling assay to measure TMB and DNA sequencing to evaluate for single nucleotide variants, insertions, deletions, and indels. Figure 2 shows the detailed results of the next-generation whole-exome sequencing report for our patient.

Given her previous response to chemotherapy and lack of clinical benefit from endocrine therapy and CDK 4/6 inhibitors, it was determined that she would benefit from the reintroduction of chemotherapy. Figure 1 shows the timeline of different treatments that the patient received along with the adverse effects experienced and disease response. Patient was treated with weekly liposomal doxorubicin and subsequently with eribulin without much evidence of disease response. In addition, her performance status continued to decline, and she was ultimately transferred to hospice care and passed away.

Discussion

Breast cancer is classified into different molecular subtypes based on the expression of ER, PR, and HER2. ER–positive breast cancer is the largest molecular subtype and can have co-expression of PR and/or HER2.[1] Treatment for ER-positive breast cancer in the metastatic setting is primarily directed toward the estrogen-ER pathway, including multiple modalities of therapy such as selective estrogen receptor modulators (SERMs), aromatase inhibitors (AIs), and selective estrogen receptor down regulators (SERDs), which all fall under the bracket of endocrine therapy, and most recently CDK4/6 inhibitors which cause cell cycle arrest.[8] Although endocrine therapy is considered the frontline treatment option in these patients based on prior clinical studies, this may not be applicable to all patients. Patients with visceral involvement and cytopenia, such as our patient, traditionally do not meet inclusion criteria for clinical trials and hence are not represented well for us to extrapolate these trial findings. Moreover, in certain cases, chemotherapy has an early onset to disease response and may be especially important for patients with higher disease burden and an urgent need for rapid disease response. This is exemplified in our case report where the need for an urgent response warranted the initiation of chemotherapy over endocrine therapy.

Current NCCN (National Comprehensive Cancer Network) treatment guidelines recommend systemic therapy in patients presenting in visceral crisis, with single agent therapy being preferred over combination therapy except in certain patients with "high tumor burden, rapidly progressing disease and visceral crisis" where combination therapy would be preferred. Choice of initial therapy depends on the patient's comorbidities, the drug's adverse effect profile, and expected tolerability. Due to the patient's poor performance status, single agent nab-paclitaxel was chosen in our patient as the initial chemotherapy of choice.

Table 1 presents published case reports and other review of literature related to patients in visceral crisis with bone marrow involvement.[9-12] Interestingly, patients were predominantly treated with chemotherapy as noted below.

Moreover, despite the success seen with endocrine therapies in ER-positive breast cancer, endocrine resistance continues to be a roadblock in achieving desired outcomes. This was noted in our patient who had clinical and biochemical progression despite the use of hormonal therapy and abemaciclib (CDK4/6 inhibitor). Endocrine resistance has been attributed to multiple culprits including diversity in the expression of estrogen receptor α (ERα) within the primary tumor and metastatic lesions,[2] loss of ERα expression,[13,14] CYP2D6 deficiency contributing to tamoxifen resistance,[15] and ERα mutations causing constitutional activation.[2,16-18]

Interestingly, our patient had multiple genomic alterations noted in her NGS test, including BRCA1 copy number loss, RET mutation, ERBB2 mutation, as well as a high TMB. She was initiated on chemotherapy with nab-paclitaxel with evidence of biochemical, radiographic, and clinical response. However, transitioning to endocrine therapy in the setting of

Table 1. Demographic and treatment characteristics of patients with metastatic breast cancer (bone marrow involvement).

TYPE OF STUDY	THERAPY	HORMONE RECEPTOR STATUS	NUMBER OF PATIENTS	RESULT REPORTED	OVERALL SURVIVAL (OS)
Case study	Low-dose capecitabine	All ER+ PR+ HER2–	5	Hematological response: 4/5	Range: 7-24+ months
Case report	Continuous doxorubicin	ER+ PR+ HER2–	1	Complete recovery of bone marrow function for 3 years	Not reported
Case report	Eribulin mesylate	ER+ PR+ HER2–	1	Hematological response after 7 cycles (7.7 months)	Not reported
Retrospective case analysis	Docetaxel/adriamycin (n = 6), gemcitabine/vinorelbine (n = 5), liposomal doxorubicin (n = 1), capecitabine (n = 1), epirubicin/cyclophosphamide (n = 3), docetaxel (n = 1), gemcitabine (n = 1), paclitaxel/5-FU (n = 1), and docetaxel/gemcitabine (n = 1)	18: ER and/or PR+ (6 ER–), 4: ER– PR– 3: HER2+, 2: Triple negative	22	Hematological improvement in 10 out of 14 anemic patients (pts), 6 out of 9 thrombocytopenic pts, all 4 leukopenic pts	Median OS: 19 months

Abbreviations: ER, estrogen receptor; HER 2, human epidermal growth factor receptor 2; OS, overall survival; PR, progesterone receptor.

Figure 1. Timeline of treatment sequence, with response and predominant adverse effect.

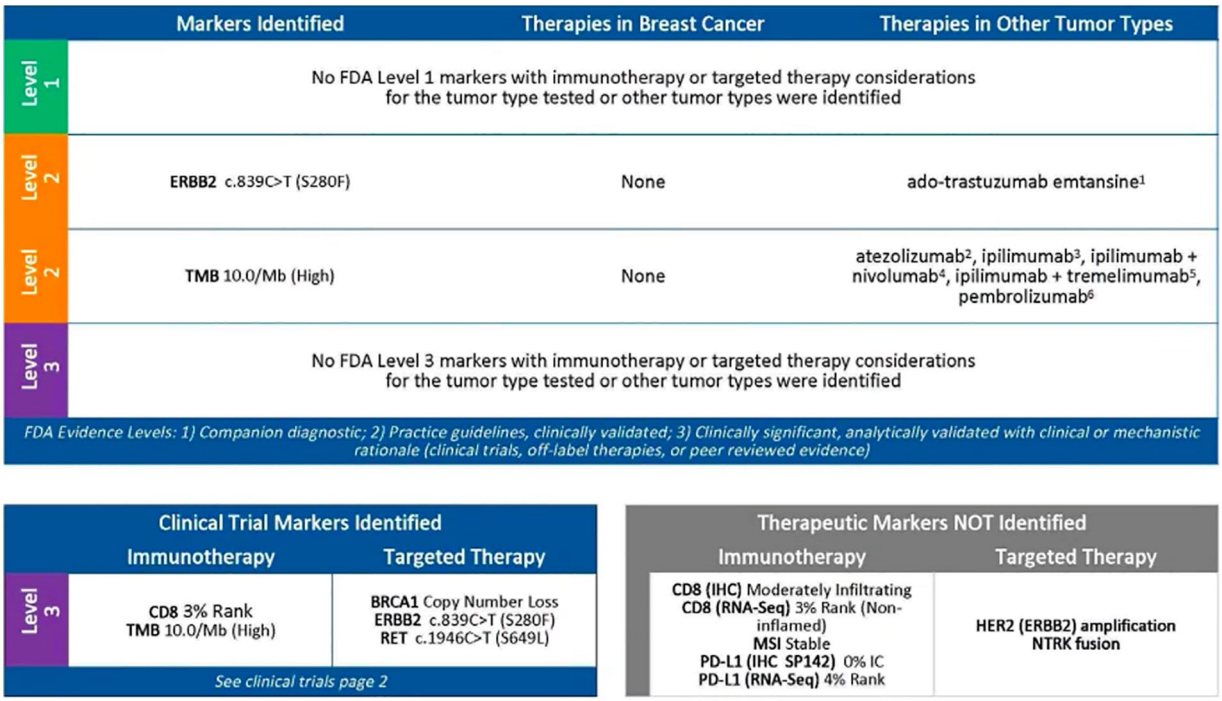

Figure 2. Next-generation whole-exome sequencing of lymph node biopsy sample revealing the presence of de novo mutation in ERBB2, RET, and BRCA1 copy number loss along with high tumor mutational burden (TMB).

nab paclitaxel-induced neuropathy led to disease progression. Some of these alterations have been associated with initial and/or subsequent endocrine resistance in literature. ERBB2 is part of the mitogen-activated protein kinase (MAPK) signaling cascade, and patients with tumors possessing MAPK mutations have been noted to have shorter progression-free survival

on aromatase inhibitors compared to those with unaffected tumors.[19] It has been shown that ERBB2 mutations could be acquired after endocrine therapy (aromatase inhibitors) in ER-positive metastatic breast cancer.[20] In addition, high TMB has been associated with metastatic invasive lobular carcinoma that is refractory to endocrine therapy.[21] RET protein expression has been linked to breast cancer recurrence after adjuvant endocrine therapy. Furthermore, RET downregulation has been associated with increased sensitivity to tamoxifen.[22] There is evidence of endocrine therapy (tamoxifen) resistance in BRCA-deficient breast cancer as the protein product of BRCA1 gene interacts with estrogen receptor to which tamoxifen binds. This tamoxifen-induced suppression of ERα transcriptional activity is blocked in BRCA-mutated breast cancer.[23] Several studies have explored the genomic landscape of metastatic tumors and their correlation with endocrine resistance. However, this information is not being used in the clinical setting as of yet, and all patients with hormone receptor–positive breast cancer, irrespective of genomic mutations, are treated with endocrine therapy in the first-line setting.

Apart from being a potential indicator of endocrine resistance and chemotherapy sensitivity, information obtained from NGS could help in guiding decisions regarding therapy directed to the genomic alteration. For example, the TAPUR (Targeted Agent and Profiling Utilization Registry) study reported the activity of Pembrolizumab in metastatic breast cancer patients with high TMB.[24] Pre-clinical mouse models with ER+ breast cancer xenografts comprising RET/GDNF stimulated cells have noted anti-tumor activity when RET inhibitors are combined with aromatase inhibitors.[25] Olaparib, a poly (ADP-ribose) polymerase (PARP) inhibitor, has been reported to have clinical activity in metastatic triple negative breast cancer with somatic BRCA1 mutation,[26] in addition to its approval for germline BRCA mutation.[27] Recently, RET inhibitor selpercatinib was approved for RET fusion-positive non-small cell lung carcinoma underscoring the importance of identifying somatic mutations. Acquired ERBB2/HER2 mutations conferring resistance to endocrine therapy could be overcome by combining endocrine therapy with HER2-directed therapy (neratinib).[20] Unfortunately, our patient developed severe diarrhea after starting abemaciclib which precluded us from initiating neratinib given its association with a similar side effect.

As standard of practice, NGS is not performed at the time of diagnosis. However, in the few cases where it is, it can provide a wealth of information about treatment options. In the setting of multiple somatic mutations that can be associated with endocrine resistance, such as our case, a "non-endocrine" therapy approach with chemotherapy or targeted therapy may be more suitable, especially in the setting of visceral crisis or high disease burden, where attempting a potential low efficacy therapy may do more harm than good, and delay clinical response.

This case emphasizes the effectiveness of chemotherapy in the setting of visceral crisis including bone marrow involvement and highlights the value of NGS in therapeutic decision making. Studies have shown a higher frequency of genomic alterations in *de novo* metastatic breast cancer compared to recurrent metastatic breast cancer.[28] Therefore, further studies on the role of genomic alterations in *de novo* metastatic breast cancer may enhance and personalize our treatment approaches in this patient population.

Conclusions

Our case of a patient with endocrine therapy resistance in the setting of multiple genomic alterations on NGS warrants a deeper look into whether patients with hormone receptor–positive metastatic breast cancer and multiple genomic alterations may benefit from an alternative treatment approach. There is a high unmet need for biomarker-driven treatment options in hormone receptor–positive breast cancer patients, especially in the presence of visceral crisis and life-threatening disease, where a rapid therapeutic approach is necessary.

Author Contributions

All the authors contributed to drafting, revising and approving the final manuscript.

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