BRAF V600E Mutation in Triple-Negative Breast Cancer: A Case Report and Literature Review

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Established Facts

- Triple-negative breast cancer is regarded as the most aggressive breast malignancy, which contributes to worse disease-free survival and overall survival.
- In triple-negative breast cancer, the usual systemic treatment is chemotherapy.

Novel Insights

- The prognosis of triple-negative breast cancer with the BRAF^{V600E} mutation is poor.
- The BRAF^{V600E} mutation may be a potential prognostic factor and therapeutic target for breast cancer.

Keywords

Triple-negative breast cancer · BRAF V600E · Heterogeneous · Resistance · Targeted therapy

Abstract

Background: The B-Raf proto-oncogene (BRAF^{V600E}) gene mutation has been identified in a variety of malignancies, but no evidence of the efficacy of vemurafenib treatment in BRAF^{V600E} mutant breast cancer (BC) has been reported.

Case Presentation: We reported a 60-year-old woman with confirmed triple-negative BC with BRAF^{V600E} mutation. Progression-free survival (PFS) for first-line chemotherapy was 7 months. The patient received vemurafenib and albumin-bound paclitaxel as second-line therapy, exhibiting regression of some pulmonary metastatic lesions with concomitant progression of other lesions, and achieved 4.4 months of PFS. Genetic testing of the progressed pulmonary lesion

revealed the BRAF^{V600E} mutation, and acquired new mutations and AR amplification. The patient ultimately died of multiple organ failure and achieved 12 months of overall survival. **Conclusions:** The BRAF^{V600E} mutation may be a potential prognostic factor and therapeutic target for BC.

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Introduction

Triple-negative breast cancer (TNBC) is a heterogeneous group of tumors comprising various breast cancers (BCs) defined as the absence of the estrogen receptor (ER) and progesterone receptor with corresponding negativity for human epidermal growth factor receptor 2 (HER-2). The primary characteristics of TNBC include younger age, higher grade and mitotic index, more advanced stage at diagnosis, and increased aggressive-

Fig. 1. NGS analysis for patient pre- and post-vemurafenib treatment: FOXA1 mutation was detected in both tissue and plasma after treatment, indicated by red box; AR gene high-fold amplification was detected in tissue after treatment, indicated by red box. NGS, next-generation sequencing; BRAF, B-Raf proto-oncogene.

ness with a higher risk of brain metastasis [1]. Due to the lack of drug-targetable receptors, the primary method for systemic management of both early-stage and metastatic settings is chemotherapy, which improves outcomes in TNBC [2]. The B-Raf proto-oncogene (BRAF) is a RAS-regulated cytoplasmic serine-threonine kinase that plays a key role in regulating the mitogen-activated protein kinase (MAPK) signal transduction pathway. The most common mutation locus is found in codon 600 of exon 15 (V600E) of the BRAF gene, causing constitutive hyperactivation, proliferation, differentiation, survival, and oncogenic transformation. However, treatment of BRAF^{V600E} mutant advanced TNBC with vemurafenib has not been reported. Herein, we report a particularly interesting case wherein genetic material obtained from primary and pulmonary metastases subjected to next-generation sequencing analysis revealed the BRAF^{V600E} mutation. The corresponding efficacy of vemurafenib as a second-line treatment for metastatic breast cancer (MBC) was also evaluated in this patient.

Case Presentation

A 60-year-old woman was initially identified as BC-positive in December 2017 and underwent right breast mastectomy and axillary lymph node dissection. Immunophenotyping was negative for ER, progesterone receptor, and HER-2, and Ki67 was 90%. No definitive finding of distant metastases was recognized. Pathological diagnosis was indicated as TNBC and stage IIA (pT1cN1M0). The patient received adjuvant chemotherapy (epirubicin and cyclophosphamide [4 cycles every 2 weeks] followed by docetaxel [4 cycles every 3 weeks]) and adjuvant radiotherapy (chest wall and regional lymph nodes). Due to lymph node metastasis, the patient was treated with capecitabine (3 cycles) as intensive treatment to reduce recurrence on August 10, 2018.

Enhanced computed tomography (CT) revealed multiple new pulmonary nodules and lymph node metastases on October 22, 2018, leading to progressive disease (PD). Biopsy of pulmonary nodules showed lung metastasis of BC. The patient received vinorelbine and cisplatin (6 cycles every 3 weeks) as first-line treatment, and the best response was stable disease. She then received oral vinorelbine and capecitabine metronomic as maintenance therapy. However, the efficacy was evaluated as PD on May 25, 2019, resulting in 7 months of progression-free survival (PFS).

Next-generation sequencing analysis of the primary tumor revealed a BRAF^{V600E} mutation and other mutations without spe-

May 25, 2019

July 18, 2019

Fig. 2. CT pretreatment (A–D): right pulmonary lesions, indicated by red arrows (A, B); left adrenal gland (C) and left kidney without tumor lesion have been marked by red arrows (D). CT post-treatment (E–H): right pulmonary lesions decreased compared to pre-treatment (E); the right pulmonary lesion was larger than that pre-treatment and has been marked by red arrow (F); the left adrenal gland (G) and left kidney had a small nodule compared to those pretreatment and has been marked by red arrows (H). CT, computed tomography.

cific targeted therapy (Fig. 1; online suppl. Table 1; for all online suppl. material, see www.karger.com/doi/10.1159/000520453). Because vemurafenib use for BC treatment is not approved in China, the patient was required to sign an informed consent form, and she received vemurafenib (960 mg twice a day, continuously) and albumin-bound paclitaxel as second-line therapy on May 30, 2019. After 1 cycle of treatment, the patient suffered from grade 4 myelosuppression, diarrhea, and oral ulcer. The second-cycle dose was adjusted to 720 mg of vemurafenib with albumin-bound paclitaxel on June 25, 2019. After 2 cycles of treatment, CT showed regression of some pulmonary metastatic lesions with concomitant progression of other lesions; thus, the efficacy was not homogeneous (Fig. 2). Because the patient refused chemotherapy, she was treated with single-dose vemurafenib (480 mg) on August 01, 2019. On August 30, 2019, CT showed regression of some metastatic pulmonary and lymph node lesions with concomitant progression of other lesions (Fig. 3).

Because the efficacy of lung lesion treatment was nonuniform, biopsy of the progressed lung lesion revealed lung metastasis of BC, and genetic testing of the lesion showed BRAF^{V600E} mutation, and acquired new mutations of PDGFRB, NF2, GRM3, MLH1, FOXA1, LRP1B, and AR amplification compared to pretreatment. Increased abundance of tumor-specific mutations (BRAF, PIK3R1, and TP53) and detection of new tumor mutations (FOXA1, PDGFRB) in the circulating tumor DNA (ctDNA) sample compared to pre-treatment (Fig. 1, 4) may be associated with tumor progression. None of these mutations had specific targeted therapy (online suppl. Table 1). AR has been proposed as a therapeutic target in ER-negative BC that retains the AR. Bicalutamide is an AR inhibitor that impairs nuclear localization of the AR; therefore, the patient was treated with bicalutamide as third-line treatment on October 12, 2019. CT showed significant progression (Fig. 5) on October 18, 2019. The patient died of multiple organ failure and achieved 12 months of overall survival (from advanced diagnosis to death).

Fig. 3. Right pulmonary lesions, indicated by red arrows (**A**, **B**); left adrenal gland lesion (**C**); left kidney lesion (**D**). **E**, **F** Right pulmonary lesions decreased compared to before (**A**, **B**), while the left adrenal gland (**G**) and left kidney (**H**) lesions were larger than those before (**C**, **D**), indicated by red arrows.

Discussion

Technological advances in DNA and RNA sequencing have promoted the discovery of biomarkers and oncogenic drivers, providing new treatment strategies for patients who lack other therapy alternatives. Precision oncology has been used to guide therapeutic decisions in the clinical management of MBC [3]. Therefore, it is important to clinically analyze tumor tissues, especially metastases. In our case, molecular analysis revealed different gene mutations. To our knowledge, the BRAF^{V600E} mutation is rare in BC. This is the first case report of vemurafenib treatment of BC with the BRAF^{V600E} mutation. BRAF plays important roles in regulating the MAPK/ERK signaling pathway and affects cell division, differentiation, and secretion [4]. The patient achieved 10 months

of disease-free survival and 7 months of PFS after first-line chemotherapy, suggesting that the cancer was insensitive to chemotherapy [5]. The patient achieved 12 months of OS, suggesting that survival is decreased with the BRAF^{V600E} mutation in MBC [6]. We speculate that BRAF^{V600E} mutation may predict a more aggressive clinical course in BC.

Tumors have generally been shown to lack intratumoral heterogeneity; however, a previous study has described heterogeneous staining and discordant results between primary and metastatic tumors [7]. In this report, except for the BRAF^{V600E} mutation in the lung metastases, the mutations in other metastatic lesions were unknown. Therefore, other less effective lesions may be BRAF wild type. Independent mutations in different tissues are possible and may occur at any time.

Fig. 4. Dynamic changes of gene mutations abundance pre- and post-vemurafenib treatment.

October 18, 2019

Fig. 5. CT showed the lesions (indicated by red arrows) of the right lung (**A**, **B**), bilateral adrenal gland (**C**), and left kidney (**D**); right abdominal wall and right extraperitoneal (**D**) had significant progression than before. CT, computed tomography.

Immune checkpoint inhibitors represent a promising treatment strategy for TNBC. Based on the IMpassion130 trial [8], atezolizumab became the first immune checkpoint inhibitor to receive BC-specific approval. However, immunotherapy is not indicated for BC in China and is only available within clinical trials. Therefore, the patient did not undergo programmed-cell death ligand-1 or combined positive score biomarker detection or immunotherapy. Poly (ADP-ribose) polymerase (PARP) 1/2 inhibitors are a class of anticancer agents that target tumor-specific defects in DNA repair. Based on the OlympiAD [9] and Embrace [10] phase III clinical trials, the US Food and Drug Administration approved olaparib and talazoparib for the treatment of patients with BRCA-mutated, HER-2-negative advanced or metastatic BC. However, our patient had no germline BRCA mutation; therefore, PARP inhibitor treatment was not considered.

Rapid recovery of MAPK pathway signaling was associated with resistance to BRAF inhibitors [11]. This can be achieved by combining BRAF and MEK inhibitors [12]. Vemurafenib is a low-molecular-weight, orally available inhibitor which selectively binds to the ATP-binding site of BRAF^{V600E} kinase and inhibits its activity. In our case, the clinical evidence for molecular targets according to the ESMO Scale of Clinical Actionability for molecular Targets [13] was tier III. Because MEK inhibitors are not available in China, the patient received vemurafenib and albumin-bound paclitaxel as second-line therapy, and achieved 4.4 months of PFS. It is hypothesized that the combination of vemurafenib and a MEK inhibitor may yield better results than vemurafenib monotherapy. Luminal androgen receptor (LAR)-positive TNBC was characterized by significant overexpression of AR-related genes (AR and FOXA1) and higher PI3K pathway protein. PI3K combined with AR inhibitors exhibited marked antitumor activity in LAR-TNBC [14]. The patient had LAR-TNBC with confirmed strong expression of AR-related genes and PIK3R1 mutation. We speculate that PI3K inhibitors combined with bicalutamide may have better efficacy. The patient acquired new mutations of unknown significance post-treatment that may be associated with tumor progression. Increased abundance of tumor-specific mutations and detection of new tumor mutations in the ctDNA sample compared to pre-treatment may be associated with tumor progression.

Conclusion

We reported the patient with varied clinical response to vemurafenib. These results suggest that it may be important to determine whether intra- and inter-tumor heterogeneity exist among primary and metastatic tumor, which may provide further details to understand the

pathogenesis of BRAF mutations in MBC and optimize treatment modalities. BRAF mutation may represent a potential predictive biomarker and therapeutic target for BC. Further study is needed to determine whether BRAF-mutated MBC has poor prognosis.

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Statement of Ethics

The study has been approved by the Ethical Committee of Sun Yat-Sen University Cancer Center (B2021-153-01). Written informed consent was obtained from the patient's next of kin for publication of this case report and any accompanying images.

Conflict of Interest Statement

There are no conflicts of interest for all authors.

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Author Contributions

F.X. was responsible for case management. F.X., L.Y.W., Q.Y.L., J.K.K., H.R.X., and S.S.W. contributed to case review. F.X. and L.Y.W. were the principal writers of the manuscript. Q.Y.L., J.K.K., H.R.X., and S.S.W. edited and provided valuable insight into the preparation of the paper. All authors read and approved the final manuscript.

Data Availability Statement

The authors declare that data supporting the findings of this study are available within the paper.

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