Combined treatment with everolimus and fulvestrant reversed anti-HER2 resistance in a patient with refractory advanced breast cancer: a case report

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Background: Everolimus, an inhibitor of the mammalian target of rapamycin, shows promising antitumor activity when combined with trastuzumab and chemotherapy for human epidermal growth factor receptor-2 (HER2)-positive breast cancer or when combined with endocrine agents for hormone receptor (HR)-positive tumors. However, data are limited regarding the effect of everolimus in combination with endocrine drugs in HER2-positive advanced breast cancer regardless of the HR status.

Case presentation: A 44-year-old female was diagnosed with recurrent HER2-positive breast cancer. The primary tumor was HR positive; however, the metastatic tumor was HR negative. The patient was resistant to classical chemotherapeutic agents and anti-HER2 treatment. Thus, the combination of everolimus and fulvestrant, a selective estrogen receptor downregulator, was chosen to reverse the resistance to anti-HER2 therapy. Indeed, the patient experienced long-term disease stabilization. Adverse events associated with the treatment were manageable by dose adjustments. We performed genetic testing of the metastatic tumor, which harbored a *PIK3CA* gene mutation but was positive for phosphatase and tensin homologue expression, which might result in resistance to the mammalian target of rapamycin inhibitor.

Conclusion: This case study indicates that combined treatment with everolimus and fulvestrant might be a viable option for the treatment of metastatic breast cancer patients who are HER2 positive and carry a *PIK3CA* gene mutation but are resistant to anti-HER2 therapy and classical chemotherapeutic agents. Further prospective randomized trials are needed to confirm this finding.

Keywords: mTOR inhibitor, *PIK3CA* gene, genetic testing, PI3K Akt mTOR pathway

Background

Everolimus is an inhibitor of mammalian target of rapamycin (mTOR) that is approved for the treatment for advanced hormone receptor (HR) positive (estrogen receptor [ER] and/or progesterone receptor [PR] positive), human epidermal growth factor receptor-2 (HER2)-negative breast cancer in postmenopausal women in combination with exemestane.

HER2 is overexpressed in 15%–20% of all cases of invasive breast cancer and is associated with aggressive disease and poor prognosis. Trastuzumab is the first biological antibody targeting HER2 receptor and is approved for the treatment of HER2-positive tumors. The PI3K/Akt/mTOR signaling pathway is important for the oncogenic function of HER2. Poor responses and resistance to HER2-directed therapy

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have been associated with activation of the PI3K/Akt/mTOR pathway.^{1,2} Several studies demonstrated that the combination of everolimus and trastuzumab with chemotherapy shows favorable clinical response and might restore sensitivity to trastuzumab in patients with HER2-positive breast cancer.^{3,4} Preclinical studies also revealed that everolimus combined with the aromatase inhibitor letrozole or selective ER down-regulator fulvestrant may restore sensitivity to hormonal therapy.⁵ However, there are no clear data regarding the effect of everolimus combined with endocrine agents without HER2-targeted therapy or chemotherapy for HER2-positive breast cancer, regardless of the HR status. In this report, we present a case of a patient with HER2-positive refractory advanced breast cancer in whom long-term disease control was achieved upon treatment with everolimus and fulvestrant.

Case presentation

A 44-year-old Chinese female with left invasive ductal breast cancer underwent a modified radical mastectomy in April 2005. The pathological stage of her cancer was T2N0M0 with

intermediate grade and lymphovascular invasion. The primary tumor was ER, PR, and HER2 positive and phosphatase and tensin homologue (PTEN) negative as determined by immunohistochemistry (IHC). The expression of ER and PR was scored according to the Allred score. HER2 status was scored as positive if >30% of tumor cells showed strong (3+) membrane staining, and PTEN status was designated as positive if tumor cells showed positive staining by IHC. The patient was treated with CAF (cyclophosphamide, adriamycin, and fluorouracil) adjuvant chemotherapy for six cycles and tamoxifen for 2 years without radiotherapy or trastuzumab. Metastases to the supraclavicular and cervical lymph nodes and left chest wall relapse were found in December 2007. Thus, the disease-free survival was 32 months.

From December 2007 to August 2012, the patient underwent multiple-line rescue treatments including several cytotoxic agents, HER2-targeted therapies, and endocrine therapies used for breast cancer (Table 1). Pretreatment biopsy and pathology results were not available. The rescue treatment was started with chemotherapy, but this was switched to endocrine drugs due to the adverse effects of

Table 1 History of treatment in the metastatic setting

Time	Emerging sites of metastatic disease	Rescued treatment regimens	Period ^a	Response (month)
Dec 25, 2007	Left chest wall, left supra- and subclavicular, and cervical lymph nodes	Capecitabine 1,000 mg/m ² PO twice daily on days 1–14 and docetaxel 80 mg/m ² IV on day 1	1 cycle	–
Jan 18 – Mar 2, 2008		Docetaxel 80 mg/m ² IV and trastuzumab 440 mg IV on day 1	2 cycles	–
Mar 5 – Apr 17, 2008		Docetaxel 80 mg/m ² IV, carboplatin 366 mg/m ² IV, and trastuzumab 330 mg IV on day 1	2 cycles	SD, TTF = 1 month for AEs
May 25, 2008 – Apr 23, 2009	Bilateral axillary lymph nodes	Anastrozole 1 mg PO daily and goserelin 3.6 mg SC every 28 days	11 months	SD, PFS = 11 months
May 7, 2009	Excision biopsy of left supraclavicular lymph node		Hormone receptors were negative by IHC, HER2 was positive by FISH	
May 19 – Jul 6, 2009		Exemestane 2.5 mg PO daily and rescued radiotherapy (left supra- and subclavicular region with 70.8 Gy in 38 fractions)	1.5 months	PR
May 18 – Jul 15, 2009	Bilateral lung	Paclitaxol 40 mg/m ² IV weekly	8 weeks	–
Jul 24, 2009 – Mar 9, 2010		Exemestane 2.5 mg PO daily and lapatinib 1,250 mg PO daily	7 months	The best response was unknown, PFS = 7 months
Mar 10 – Apr 22, 2010		Gemcitabine 1,000 mg/m ² IV and lobaplatin 33 mg/m ² IV on day 1	2 cycles	PD
Apr 23 – Jul 29, 2010		Vinorelbine 25 mg/m ² IV weekly for 2 weeks followed by 1 week rest	4 cycles	SD, TTF = 3 months
May 11, 2010 – Mar 15, 2011		Cytokine-induced killer cell immunotherapy, every 2 months	10 months	–
Sep 2 – Oct 11, 2010		Capecitabine 1,000 mg/m ² PO twice daily on days 1–14	2 cycles	PD
Oct 12, 2010		Vp-16 100 mg/m ² PO daily on days 1–14	1 cycle	TTF = 0.5 month
Nov 10, 2010 – Mar 10, 2011		Trastuzumab 440 mg IV on day 1 and megestrol 160 mg PO daily	5 cycles	SD, PFS = 4 months

(Continued)

Table 1 (Continued)

Time	Emerging sites of metastatic disease	Rescued treatment regimens	Period ^a	Response (month)
Apr 8 – Sep 5, 2011	Mediastinal and bilateral hilar lymph nodes, ninth thoracic vertebra	Nab-Paclitaxel 260 mg/m ² IV and trastuzumab 440 mg IV on day 1	6 cycles	SD, PFS =5 months
Sep 19 – Oct 30, 2011	Liver	Pemetrexed 500 mg/m ² IV and trastuzumab 440 mg IV on day 1	2 cycles	PD
Nov 9 – Dec 17, 2011	Intracranial	Whole-brain radiotherapy with Dt 40 Gy in 20 fractions	1 month	PR
Nov 11, 2011 – Feb 29, 2012		Capecitabine 1,000 mg/m ² PO twice daily days 1–14 and Lapatinib 1,000 mg PO daily	5 cycles	SD, PFS =3.5 months
Feb 21 – Mar 12, 2012		Vinorelbine and trastuzumab	1 cycle	PD
Mar 12 – Apr 22, 2012		Toremifene and trastuzumab	2 cycles	PD
Apr 27 – Aug 15, 2012		Docetaxel and avastin (9.1 mg/kg)	5 cycles	SD, PFS =4 months
Aug 25, 2012 – Jun 24, 2013		Everolimus and fulvestrant	10 months	SD, PFS =10 months
Jun 7, 2013	Pleura fluid extraction			Adenocarcinoma by pathology, tumor genetic testing
Jun 27, 2013	Core needle biopsy of liver lesions			A few suspicious cells which are difficult for diagnosis
Jun 26 – Jul 16, 2013		Trastuzumab emtansine 3.6 mg/kg IV day 1	1 cycle	PD
Aug 1 – Aug 20, 2013		Sorafenib 200 mg PO twice daily for 20 days	3 weeks	PD
Aug 20 – Oct 27, 2013 (Death)		Palliative treatment	2 months	PD

Notes: ^aCycled every 21 days. From the date of diagnosis to March 2011, the patient was treated in other hospitals in the People's Republic of China, and thus, several responses to regimens were unknown (shown as “–”). Then, the patient received rescue treatment in our hospital (Hospital of Academy of Military Medical Sciences) from April 2011 to August 2013.

Abbreviations: SD, stable disease; PR, partial response; HER2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; FISH, fluorescence in situ hybridization; PD, progressive disease; TTF, time to treatment failure; PFS, progression-free survival; PO, per os; IV, intravenous; SC, subcutaneous; Gy, grays; AE, adverse event; IHC, immunohistochemistry.

chemotherapy. The patient obtained clinical benefit from endocrine therapy. The recurrent tumor in the left supra-clavicular lymph nodes was HR negative by IHC and HER2 positive by fluorescence in situ hybridization detection in two hospitals in May 2009. Then, chemotherapy and HER2-directed therapy as main choices were applied, and endocrine therapy was also used due to the intolerance or lack of response to chemotherapy. Among these regimens, two regimens provided clinical benefit, namely, anastrozole combined with goserelin for 11 months and exemestane plus lapatinib for 7 months during the earlier treatment. In contrast, a total of seven regimens containing trastuzumab and two regimens containing lapatinib all failed (Table 1).

After discussion of various therapeutic options including palliative care, in 2012, we decided to treat the patient with everolimus (5 mg/d orally) in combination with intramuscular fulvestrant (500 mg once/28 days). The response and side effects of the regimen are shown in Table 2. After 6 days, we increased the dose of everolimus to 10 mg/d for 34 days.^{6,7} Measurable lung lesions diminished modestly as observed by computed tomography (CT) examination (Figure 1). The changes in target lesions based on the maximum reduction of the sum of lesion diameters are shown in Figure 2. Side effects included third-degree stomatitis and liver toxicity and second-degree hematologic toxicity. After discontinuation of everolimus for 10 days, the side effects

were relieved and eventually disappeared. When the patient took 5 mg everolimus daily, the lung lesions increased slightly. We therefore increased the dose to 5 and 10 mg/d alternately, with an estimated daily dose of 7.5 mg, and the lesions diminished again. Subsequently, everolimus was reduced to 5 mg daily or treatment was discontinued due to fatigue and other adverse events. Treatment was resumed again at 5 and 10 mg/d alternatively and after approximately six months of treatment, the patient could tolerate the full dose (10 mg/d) of everolimus.

At the first appearance of tumor progression detected by CT on June 7, 2013, the patient's pleural effusion was extracted for pathologic examination and molecular profile testing (performed by Caris Life Sciences, Irving, TX, USA). The results confirmed that the tumor was a HR-negative, HER2-positive adenocarcinoma that contained a *PIK3CA* gene mutation and was positive for PTEN expression (Table 3). The patient continued everolimus treatment until disease progression was confirmed on June 24, 2013. The response was stable disease as evaluated by Response evaluation criteria in solid tumors, and progression-free survival (PFS) was 10 months. Thereafter, the patient was treated with trastuzumab, emtansine, and sorafenib, individually, with no measurable responses. The patient died on October 27, 2013, with overall survival time of 102 months. Written informed consent was obtained from the patient for publication of this

Table 2 Treatment and side effects of everolimus combined with fulvestrant

Time	Dose of everolimus	Response	Side effect ^a
Aug 25 – Aug 30, 2012	5 mg/d for 6 days	SD	Third-degree stomatitis; Third-degree liver toxicity (AST 359 U/L, ALT 632 U/L); Second-degree thrombocytopenia; First-degree leukopenia
Aug 31 – Oct 3, 2012	10 mg/d for 34 days		
Oct 4 – Oct 12, 2012	Drug withdrawal		The side effects were relieved to 0 or first-degree grade with discontinuation of everolimus for 10 days.
Oct 13 – Nov 6, 2012	5 mg/d	SD	First-degree leukopenia; First-degree increased AST and ALT
Nov 7 – Dec 31, 2012	5 and 10 mg/d alternately	SD	Second-degree fatigue; First-degree palpitation; First-degree increased AST; Second-degree increased ALT
Jan 1 – Jan 25, 2013	5 mg/d	SD	First-degree increased AST and ALT
Jan 26 – Feb 8, 2013	5 and 10 mg/d alternately		First-degree fatigue
Feb 8 – Feb 17, 2013	Drug withdrawal during holiday		First-degree fatigue
Feb 17 – Mar 10, 2013	5 and 10 mg/d alternately	SD	Second-degree fatigue; Second-degree decreased appetite; First-degree stomatitis; First-degree nausea; First-degree hypokalemia
Mar 10 – Jun 24, 2013	10 mg/d	SD, PFS =10 months	Second-degree fatigue; Second-degree decreased appetite; First-degree stomatitis; First-degree increased AST and ALT; First-degree nausea; First-degree hypokalemia; First-degree hypocalcemia

Notes: ^aSide effects were graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, Version 3.0.

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; PFS, progression-free survival; SD, stable disease.

Figure 1 Chest computed tomography images showing the response to everolimus combined with fulvestrant.

Notes: Compared to lung lesions at baseline (A) lesions at the level of main bronchus and (B) lesions at the level of right middle bronchus and left lower lobar bronchus, (C and D) show a modest decrease in the size of the metastatic bilateral lung lesions treated with 1 month of orally administered 10 mg/d everolimus plus fulvestrant.

Figure 2 Response to everolimus treatment.

Case Report and any accompanying images. This case report was approved by the Ethics Committee of Affiliated Hospital of Academy of Military Medical Sciences.

Discussion

The patient described in this report was premenopausal and presented with a HR-positive tumor, which is quite common among Asian women with early breast cancer. She experienced tumor relapse, probably due to the lack of adjuvant trastuzumab treatment, which was not yet routinely used in the People's Republic of China in 2005. Receptor conversion has been confirmed in 18%–54% of breast cancer patients.⁸ Thus, biopsy of metastasized sites is likely to provide useful information that may influence the therapeutic strategy. In this case, the HR status was positive in the primary tumor but negative in the metastatic tumors.

In the early period of metastasis, endocrine drug-containing therapy achieved long-term tumor control, and the possible reasons are as follows: 1) the high heterogeneity of breast cancer, which suggests the presence of endocrine-sensitive cells; 2) the possible existence of variation in HR status in the

metastatic stage (although we have no IHC data for the tumor prior to treatment); and 3) slow tumor progression and a light tumor load with only local lymph node metastases. Later, the patient became resistant to endocrine therapy combined with HER2-directed therapy, and the tumor was confirmed to be HR negative twice.

Preclinical studies revealed that everolimus combined with the aromatase inhibitor letrozole or selective ER down-regulator fulvestrant could reverse Akt-mediated resistance and restore sensitivity to hormonal therapy.⁵ In a Phase II study, 31 patients with ER-positive metastatic breast cancer who had progressed while treated with an aromatase inhibitor received everolimus in combination with fulvestrant.⁹ The EFECT trial served as the historical control for the effect of single-agent fulvestrant, with a median time to progression of 3.7 months.¹⁰ The clinical benefit rate was 49%, and the median time to progression of everolimus plus fulvestrant was 7.4 months (95% confidence interval, 1.9–12.1). Although two patients with HER2-positive disease were included in the EFECT trial, their responses were not reported.

Inhibition of the PI3K/Akt/mTOR pathway in breast cancer is a novel and valid choice for ER-positive and/or HER2-positive tumors. The patient described in this study was resistant to ~20 lines of therapy; therefore, the combination of everolimus and fulvestrant was chosen to reverse the resistance to anti-HER2 therapy. Everolimus has been evaluated in several Phase I/II clinical studies in unselected or HER2-negative metastatic breast cancer patients and exhibited modest results as a single agent with an overall response rate ranging from 0% to 21.2%.^{11–13} Studies confirmed that important cross talk exists between the ER and HER2 pathways. Because the efficacy of everolimus combined with HER2-directed agents was better in patients with ER-negative cancer than in patients with ER-positive cancer,⁴ we speculated that inhibition of both the PI3K/Akt/mTOR pathway by everolimus and the ER pathway by fulvestrant could result in strong antitumor activity.

We demonstrated that the recurrent tumor was HR negative and HER2 positive, had a *PIK3CA* mutation in exon 20, and expressed PTEN as shown by IHC. Studies have indicated that tumors with *PIK3CA* mutations and loss of PTEN exhibit PI3K/Akt/mTOR pathway activation and respond to mTOR inhibitors.^{4,14} Therefore, the present case demonstrated that the clinical benefit might be due to the *PIK3CA* somatic mutation. Because PTEN leads to downregulation of the *PIK3CA*/Akt pathway, the tumor may become resistant to mTOR inhibitor treatment.

Everolimus is recommended at a dose of 5 mg/d when combined with chemotherapy and at a dose of 10 mg/d when

Table 3 Tumor genetic testing results (metastatic pleura fluid)

Gene	Method	Result	Value
ER	IHC	Negative	–, 0%
PR	IHC	Negative	–, 0%
HER-2	CISH	Amplified	signal counts: 14.54
	IHC	Positive	+++ , 90%
PIK3CA	Next Gen SEQ	Pathogenic	H1047R mutation
PTEN	IHC	Positive	+, 60%
TOP2A	FISH	Not amplified	copy number: 1.07
C-KIT	Next Gen SEQ	Wild-type	N/A
BRAF	Next Gen SEQ	Wild-type	N/A

Notes: – indicates negative value; +++ indicates highly positive value; + indicates positive value.

Abbreviations: IHC, immunohistochemistry; Next Gen SEQ, next generation sequencing; CISH, chromogenic in situ hybridization; FISH, fluorescence in situ hybridization; N/A, not applicable.

combined with endocrine agents.^{4,11,12} The most common adverse events associated with everolimus are stomatitis, rash, fatigue, and diarrhea.^{6,15} Most of the toxicities experienced by our patient were Grade 1 or 2; however, the patient experienced Grade 3 stomatitis and liver toxicity soon after the dose of everolimus was increased to 10 mg/d. The toxicities were reduced to Grade 1 after the dose was lowered to 5 mg/d or treatment was discontinued. After approximately 6 months of treatment, the patient experienced tolerable toxicities on the full dose of everolimus.

The response improved with increased everolimus dosage, and the tumor size slightly increased with dosage reduction. These findings suggest the existence of a dose–effect relationship. However, the pharmacokinetics of everolimus with or without any agents has not been evaluated for a large population of Asian patients.¹⁶ Although early studies indicated that age, sex, and weight have no effect on pharmacokinetics parameters, the best dose of everolimus for the population with a low body surface area is uncertain. In subgroup analyses of BOLERO-2, everolimus plus exemestane improved PFS by 8.48 months in Asian patients and 7.33 months among non-Asian patients.¹⁵ Although we can only speculate that such good efficacy is associated with the use of a high dose, the present case indicated that the appropriate dose intensity for everolimus might be 5–7.5 mg/d in the initial stage for Asian women and patients who have received multiple-line therapies with low weight and poor performance status.

Conclusion

This case indicates that everolimus in combination with fulvestrant has promising antitumor activity in HER2-positive breast tumors that harbor *PIK3CA* mutations, regardless of the HR status. The adverse events associated with everolimus could be well managed by dose reduction or discontinuation of everolimus. Genetic testing of metastatic tumor revealed the activation of the PI3K/Akt/mTOR pathway, and the response was in accordance with the results of genetic testing. The appropriate dose of everolimus in Asian metastatic breast cancer patients deserves further study. Further prospective randomized trials are needed to confirm the findings in this particular patient.

Disclosure

The authors report no conflicts of interest in this work.

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