International Cancer Conference Journal (2018) 7:142–147
https://doi.org/10.1007/s13691-018-0339-9

CASE REPORT

Tamoxifen withdrawal in women with progressive metastatic breast cancer: a case series of six patients

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Received: 7 June 2018 / Accepted: 31 July 2018 / Published online: 6 August 2018

Abstract

Estrogen receptor (ER)-positive metastatic breast cancers after a period of response to tamoxifen develop resistance, and the disease progresses clinically. Domination of partial agonistic activity of tamoxifen over its antagonist activity has been implicated as one of the mechanisms for acquired tamoxifen resistance. Six patients with ER-positive, human epidermal growth factor receptor 2 (HER2)-negative metastatic breast cancer who were treated with tamoxifen withdrawal were retrospectively reviewed. Three patients were premenopausal and three were postmenopausal at the beginning of this treatment. Three patients had stage IV disease and three had recurrent breast cancers with median disease-free intervals of 153 months. The treatment lines of tamoxifen therapy were first-line in two, second-line in two, and third-line in one patient. One patient had relapsed during adjuvant tamoxifen therapy. The median duration of tamoxifen therapy was 16 months. The metastatic disease sites at the time of tamoxifen withdrawal were lymph nodes in six, bone in three, chest wall in one, lung in two, pleura in one, and liver in one patient. The median duration of tamoxifen withdrawal was 6.5 months (range 5–> 23 months). Five of six patients had clinical benefits with tamoxifen withdrawal: partial response in one, long stable disease (SD) in four, and SD in one patient. Five patients were treated with aromatase inhibitors after tamoxifen withdrawal. Two patients had metastatic lymph nodes examined by multi-gene panel testing, and both of their tumors had the *AKT*1 E17K somatic mutation. One patient also had a *BRCA*1 germline mutation. Tamoxifen withdrawal at the time of tumor progression while on treatment might be an important treatment option, especially for women with highly endocrine-responsive disease.

Keywords Metastatic breast cancer · Endocrine therapy · Tamoxifen · Withdrawal

Abbreviations

QOL	Quality of life
ER	Estrogen receptor
HER2	Human epidermal growth factor receptor 2
PR	Partial response
SD	Stable disease
PD	Progressive disease
CT	Computed tomography

Introduction

The purpose of treatment for metastatic breast cancer is prolongation of survival while maintaining or improving quality of life (QOL) [1]. Endocrine therapy for estrogen receptor (ER)-positive breast cancer is one of the earliest molecular targeting therapies. The clinical benefit rate for highly endocrine-responsive tumors might be 70–80% in patients treated with endocrine therapy [1]. Moreover, endocrine therapy causes no severe adverse events and maintains QOL. However, the development of resistance to endocrine therapy is a common problem for patients with ER-positive metastatic breast cancer. Regression of tumors on cessation of tamoxifen therapy, and the resultant clinical benefits, have been reported in several case reports and study series [2, 3]. Besides the predominant role of alternative signaling pathways, domination of partial agonistic activity of tamoxifen over its antagonistic activity has been implicated as one of the mechanisms for acquired resistance to tamoxifen [4, 5]. We recently experienced six patients with ER-positive

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Table 1 Patient and tumor characteristics and treatments

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Age at the start of TAM withdrawal, years (menopausal status)	66 (post)	76 (post)	50 (pre)	69 (post)	37 (pre)	43 (pre)
Stage at the initial diagnosis of breast cancer	T2N0M0, stage IIA	T2N0M0, stage IIA	T2N2M0, stage IIIA	T2N3M1, stage IV	T4bN2M1, stage IV	T4bN3M1, stage IV
Histopathology	IDC	IDC	IDC	IDC	IDC	IDC
Subtype (ER/PgR/HER2/Ki67)	ER + PgR+ HER2− (breast) ER 90%[a] PgR 70%[a] HER2 1+[b] (lymph node)	ER + PgR+ (breast) ER 100%[a] PgR 60%[a] HER2 1+[b] (chest wall)	ER 90%[a] PgR 50%[a] HER2 2+[b], FISH no amplification (breast)	ER 100%[a] PgR 20%[a] HER2 1+[b] Ki67 24%[c] (breast)	ER 100%[a] PgR 20%[a] HER2 1+[b] Ki67 20%[c] (breast)	ER 80%[a] PgR 50%[a] HER2 0[b] Ki67 57%[c] (breast)
Adjuvant endocrine therapy	TAM (2 years)	Fadrozole (2 years)	TAM (4 years 8 months)	–	–	–
(Neo) adjuvant chemotherapy	UFT (2 years)	UFT (2 years)	FEC, DTX	–	–	–
Disease-free interval	20 years 7 months	12 years 9 months	4 years 8 months	–	–	–
Metastatic sites at the start of first-line therapy for metastatic breast cancer	Lymph node	Chest wall	Lymph node (right neck)	Lymph node Pleura	Lymph node Bone	Lymph node Bone
Previous therapies for metastatic breast cancer prior to TAM	ANA (1 year)	1. LET (4 years) 2. EXE (2 years 9 months)	–	ANA (1 year)	–	–
Treatment line of TAM therapy	Second line	Third line	Adjuvant	Second line	First line	First line
Duration of TAM therapy	4 years 5 months	1 year	4 years 8 months	1 year	1 years 8 months (+LHRHa)	5 months (+LHRHa)
Response to TAM	Long SD	PR	–	Long SD	PR	SD
Metastatic sites at the start of TAM withdrawal	Lymph node Bone Lung	Chest wall Liver	Lymph node	Lymph node Pleura Lung	Lymph node Bone	Lymph node Bone
Duration of TAM withdrawal	> 1 years 11 months	9 months	6 months	6 months	5 months (LHRHa only)	7 months (LHRHa only)
Response to TAM withdrawal	Long SD	Long SD	Long SD	PR	SD	Long SD
Reason for discontinuation of TAM withdrawal	Ongoing TAM withdrawal	PD (liver metastasis)	Patient's preference	PD (new legion in the liver)	Increase of tumor markers (patient's preference)	PD (new legion in the contralateral breast)

Table 1 (continued)

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6
Treatment after TAM withdrawal		1. ANA (3 months) 2. FUL (5 months) 3. Chemotherapy	1. LET (1 years 2 months) 2. FUL	1. EXE (9 months) 2. FUL (6 months) 3. High dose TOR (3 months) 4. Chemotherapy	1. LHRHa + ANA (> 1 years 4 months)	1. LHRHa + ANA (> 7 months)
Multi-gene panel testing	*AKT*1 E17K (lymph node; before TAM)	Not done	*BRCA*1 Q1447fs, *AKT*1 E17K, *NF*1 W561* (lymph node; after TAM withdrawal)	Not done	Not done	Not done

IDC invasive ductal carcinoma, *FISH* fluorescent in situ hybridization, *TAM* tamoxifen, *FEC* fluorouracil epirubicin cyclophosphamide, *DTX* docetaxel, *ANA* anastrozole, *LET* letrozole, *EXE* exemestane, *LHRHa* luteinizing hormone-releasing hormone analog, *FUL* fulvestrant, *EVE* everolimus, *TOR* toremifene, *PR* partial response, *SD* stable disease, *PD* progressive disease

[a]Percentage of cells showing positive nuclear staining

[b]Score

[c]Labeling index

metastatic breast cancer in whom tamoxifen withdrawal was effective.

Case reports

Six patients with ER-positive, progesterone receptor-positive, HER2-negative metastatic breast cancer who were treated with tamoxifen withdrawal between 2014 and 2018 were retrospectively reviewed (Table 1). Three patients were premenopausal and three were postmenopausal at the beginning of this treatment (Table 2). All breast cancers were invasive ductal carcinomas. Three patients had stage IV disease and three had recurrent breast cancers with median disease-free intervals of 153 months. The median duration of previous endocrine therapies for metastatic breast cancer prior to tamoxifen was 12 months (range 12–81 months) in three patients who received tamoxifen as second or third lines. The median number of lines of therapy prior to tamoxifen therapy was 2 (range 1–3), except in one patient who had relapsed during adjuvant tamoxifen therapy. The median duration of tamoxifen therapy was 16 months (range 5–56 months). In five patients who received tamoxifen for metastatic breast cancer, partial response (PR) was seen in two patients, long stable disease (SD) in two, and SD in one patient.

The metastatic disease sites at the time of tamoxifen withdrawal were lymph nodes in five patients, chest wall in one, bone in three, lung in one, pleura in one, and liver in one patient. Zoledronic acid or denosumab had been given for patients with bone metastases (Cases 1, 5 and 6). The median duration of tamoxifen withdrawal was 6.5 months (range 5–20 months). Five of six patients had clinical benefits with tamoxifen withdrawal: PR in one patient, long SD in four, and SD in one patient. Tumor markers (CEA and CA15-3) did not increase during withdrawal therapy and were effective in all patients. Representative computed tomography (CT) images are shown in Fig. 1 (Case 1) and Fig. 2 (Case 4). Although one patient (Case 3) stopped tamoxifen withdrawal while maintaining long SD because of her preference, withdrawal of tamoxifen was well tolerated.

All of the patients received endocrine therapy after tamoxifen withdrawal; five patients were treated with aromatase inhibitors. Two patients (Cases 1 and 3) had metastatic lymph nodes examined by multi-gene panel testing, and both of their tumors had the *AKT*1 E17K somatic mutation (Table 1). Case 3 also had a *BRCA*1 germline mutation (Q1447fs). Both of the lymph nodes were ER-positive and HER2-negative.

Table 2 Summary of six patients

Median age at the start of tamoxifen withdrawal, years (range)	58 (37–76)
Premenopausal	$n=3$
Postmenopausal	$n=3$
Histopathology	
Invasive ductal carcinoma	$n=6$
Subtype	
ER-positive, PgR-positive, HER2-negative	$n=6$
Stage IV	$n=3$
Recurrence	$n=3$
Median disease-free interval, months (range)	153 (56–247)
Median duration of previous endocrine therapies for metastatic breast cancer prior to tamoxifen therapy, months (range)	$n=3$, 12 (12–81)
Treatment line of tamoxifen therapy	
Adjuvant	$n=1$
First line	$n=2$
Second line	$n=2$
Third line	$n=1$
Median duration of tamoxifen therapy, months (range)	16 (5–56)
Response to tamoxifen therapy for metastatic breast cancer	
PR	$n=2$
Long SD	$n=2$
SD	$n=1$
Metastatic sites at the start of tamoxifen withdrawal	
Lymph node	$n=5$
Chest wall	$n=1$
Bone	$n=3$
Lung	$n=2$
Pleura	$n=1$
Liver	$n=1$
Median duration of tamoxifen withdrawal, months (range)	6.5 (5–>23)
Response to tamoxifen withdrawal	
PR	$n=1$
Long SD	$n=4$
SD	$n=1$
Response to endocrine therapy after tamoxifen withdrawal	
Long SD	$n=3$
SD	$n=1$
PD	$n=1$

Discussion

We report a case series of six patients who obtained significant and sustained clinical benefits on "withdrawal" from tamoxifen. Although new endocrine therapy strategies combining molecular targeting agents have been developed, the sequential therapy with endocrine agents alone might still be a useful and appropriate therapy for patients with highly endocrine-responsive disease in ER-positive, HER2-negative metastatic breast cancer [1]. There is no doubt that endocrine therapy alone can maintain QOL and is inexpensive compared to combination therapy with novel targeting agents such as CDK 4/6 inhibitors, everolimus, and PI3K inhibitors [6, 7]. Therefore, identifying patients who should receive molecular targeting agents, and those who could be given endocrine therapy alone is required.

A tamoxifen-stimulated breast tumor has been developed after long-term antiestrogen administration in vivo [8]. Mechanistic studies on selective ER modulator (SERM) stimulated growth demonstrated that tamoxifen functioned as an agonist to enhance the non-genomic activity of ER and activate focal adhesion molecules to further increase phosphorylation of IGF-1Rb [4, 5]. Furthermore, a previous study reported that tamoxifen resistance was associated

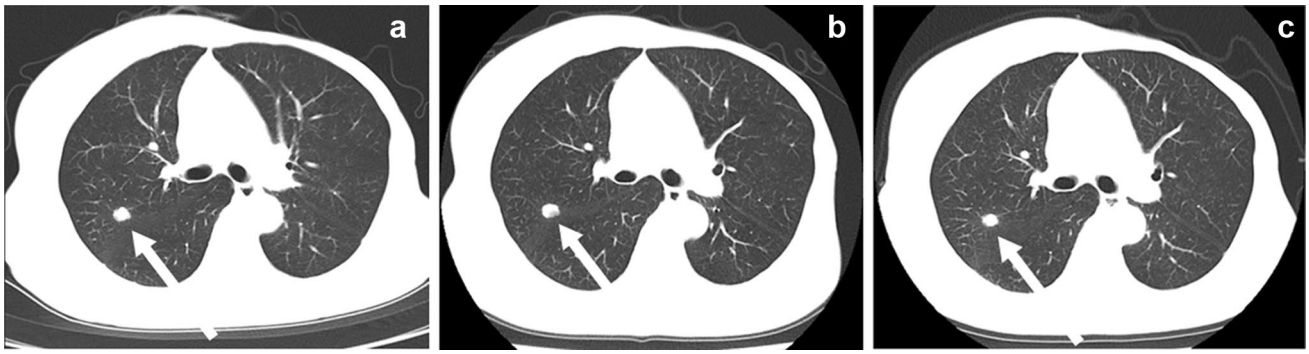

Fig. 1 A 66-year-old woman with recurrent breast cancer (Case 1). A metastatic tumor (10×8 mm) in the upper lobe of the lung was detected by CT when tamoxifen therapy was stopped (**a**). Two months after tamoxifen withdrawal, the tumor (11×8 mm) was not increasing (**b**). Five months after tamoxifen withdrawal, the tumor (10×8 mm) was not increasing and SD was maintained (**c**)

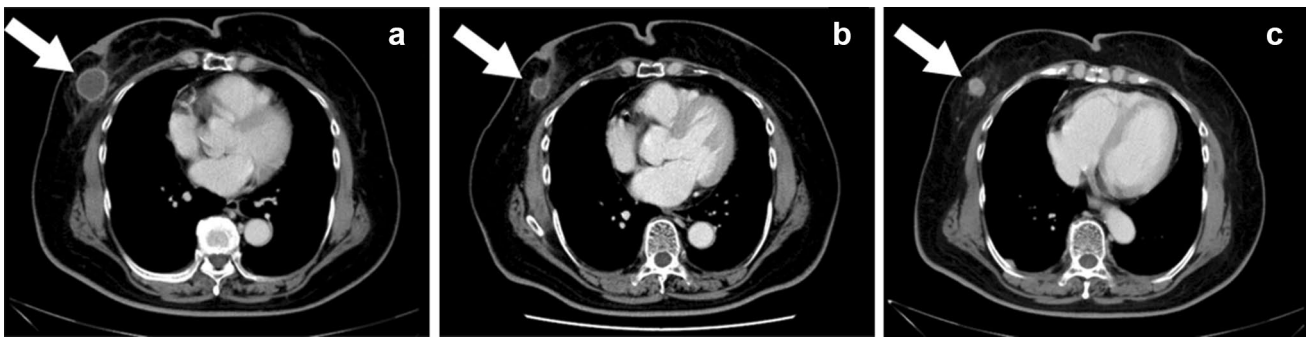

Fig. 2 A 69-year-old woman with Stage IV breast cancer (Case 4). A primary tumor (30×25 mm) in the right breast was detected by CT when tamoxifen therapy was stopped (**a**). One and a half months after tamoxifen withdrawal, the tumor size (20×15 mm) had decreased (**b**). Five months after tamoxifen withdrawal, the tumor (18×15 mm) was not increasing (**c**)

with altered estrogen receptor expression especially on the plasma membrane, including the alternative G-protein coupled receptor GPR-30 and estrogen receptor splice products, such as ERα36 [9]. It has been suggested that tamoxifen may stimulate tumor growth under certain circumstances, because withdrawal of the treatment results in a change from tumor growth to tumor regression or stabilization. Howell and colleagues reported a tumor response after withdrawal of tamoxifen in advanced breast cancer [2]. In their series, one of seven patients had a withdrawal response when adjuvant tamoxifen therapy was stopped at the time of relapse. In 65 patients treated with withdrawal after cessation of tamoxifen as first-line therapy for advanced disease, there were 5 (8%) PR and 14 (22%) SD with a median duration of withdrawal of 10 months (range 3–40 months). These investigators also showed that withdrawal effects were seen mainly in soft tissue disease, but two patients had metastatic sites in lung and two in bone. Withdrawal of endocrine therapy might have been a common strategy in women with ER-positive advanced breast cancer, especially before the introduction of aromatase inhibitors in clinical practice. Furthermore, a recent phase II trial of aromatase inhibitor withdrawal in women with progressive metastatic breast cancer while on aromatase inhibitor therapy showed a clinical benefit rate of 46% [10].

On the other hand, tamoxifen has been the most recommended endocrine agent in adjuvant endocrine therapy in premenopausal ER-positive early breast cancer. Moreover, tamoxifen in combination with ovarian function suppression has been the most recommended first-line endocrine treatment in premenopausal ER-positive metastatic breast cancer. "Withdrawal" after progression while on adjuvant tamoxifen or failure of tamoxifen as first-line endocrine therapy for metastatic disease might be an important treatment option, especially for premenopausal women with highly endocrine-responsive disease.

We recently reported in patients with late recurrence, that the involvement of metastasis in only one organ at relapse, a long duration of first-line endocrine therapy, and a long total duration of endocrine therapies after relapse significantly improved post-relapse survival [11]. Moreover, expression levels of ER in primary breast tumors were significantly higher in patients with a duration of first-line endocrine therapy > 6 months than in those with a duration

≤ 6 months [11]. The expression level of ER was higher than 80% in all of the primary tumors in our series. Furthermore, metastatic lymph nodes examined by multi-gene panel testing in two patients had the *AKT*1 E17K somatic mutation. It is not clear whether this mutation had been a driver for the metastatic diseases; both tumors were highly endocrine responsive. Understanding the response to endocrine therapy and survival in metastatic ER-positive breast cancer is critical to develop appropriate treatment strategies for individual patients.

Compliance with ethical standards

Conflict of interest The authors declare no conflict of interest.

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