Original Article

Clinical outcomes with first-line chemotherapy versus endocrine therapy for adjuvant endocrine therapy-resistant metastatic breast cancer

Bin Shao[1#], Yanlian Yang[2], Jinrong Qu[3#], Huiping Li[1], Guohong Song[1], Lijun Di[1], Hanfang Jiang[1], Ying Yan[1], Huan Wang[1], Xiaoran Liu[1], Jing Wang[1], Weiyao Kong[1]

[1]Department of Medical Oncology, Key laboratory of Carcinogenesis and Translational Research (Ministry of Education), Peking University Cancer Hospital & Institute, Beijing 100142, China; [2]CAS Key Laboratory of Standardization and Measurement for Nanotechnology, CAS Center for Excellence in Nanoscience, National Center for Nanoscience and Technology, Beijing 100190, China; [3]Department of Oncology and hematology, Shijiazhuang Third Hospital, Shijiazhuang 050011, China

Contributions: (I) Conception and design: All authors; (II) Administrative support: H Li, G Song, L Di; (III) Provision of study materials or patients: All authors; (IV) Collection and assembly of data: B Shao, J Qu; (V) Data analysis and interpretation: B Shao, J Qu, H Li; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]These authors contributed equally to this work.

Correspondence to: Huiping Li. Beijing Cancer Hospital, 52 Fucheng Road, Haidian District, Beijing 100142, China.
Email: huipingli2012@hotmail.com.

Background: Endocrine therapy resistance (ETR) is a great obstacle in the treatment of estrogen receptor-positive (ER+)/human epidermal growth factor receptor 2-negative (HER2–) breast cancer. Patients with ETR have significantly decreased clinical benefit from endocrine therapy (ET). Therefore, it is quite important to find the clinicopathological factors that affect the outcome of patients with ETR in clinical practice.

Methods: We screened 405 consecutive ER+/HER2– metastatic breast cancer (MBC) patients who were treated from 2013–2015 in our hospital. Patients with ETR (defined as relapse during adjuvant ET or within 12 months after completing adjuvant ET) were selected to explore the clinicopathological factors affecting the objective response rate (ORR) and progression-free survival (PFS).

Results: We included 135 patients in the study. Chemotherapy (CT) was administered to 96 patients and ET to 39 patients as first-line treatment. Patients with liver or visceral metastasis received CT significantly more frequently than ET (P=0.001, 0.001). There was no significant difference in median PFS between the two groups (ET: 11.8 months, CT: 12.0 months, P=0.667, HR =1.029). However, patients with more than two metastatic sites had a shorter PFS than patients with less than or equal to two metastatic sites (7.5 *vs.* 14.5 months, P=0.031, HR =1.714). When patients on CT were further stratified, those who received ET as maintenance therapy had a longer PFS (14.3 months) compared with those that did not (7.5 months) (P=0.003).

Conclusions: ET and CT were both appropriate treatments for patients with ETR. Maintenance ET was a good choice for ER+/HER2– patients.

Keywords: Endocrine resistance; ER+/HER2–; metastatic breast cancer (MBC); endocrine therapy (ET); chemotherapy (CT)

Submitted Jan 28, 2018. Accepted for publication May 11, 2018.
doi: 10.21037/tcr.2018.05.43
View this article at: http://dx.doi.org/10.21037/tcr.2018.05.43

Introduction

Breast cancer has the highest incidence and is second in mortality rate of any cancer among women (1). A high percentage of breast cancers, 50–70%, are hormone receptor-positive (HR+)/human epidermal growth factor receptor 2-negative (HER2–) (2,3). The main cause of death from breast cancer is metastasis, which develops in 20–30% of patients with early-stage breast cancer and in 6–10% of newly diagnosed breast cancer cases (4,5).

Metastatic breast cancer (MBC) is not a curable disease; therefore, the goal is to prolong survival and maintain patient quality of life. Typically, there are two treatment options for HR+/HER2– MBC patients, endocrine therapy (ET) and chemotherapy (CT) (6). The recommendation for treating patients with ET as first-line therapy was essentially based on a previous study (7). Results from that study showed that there was no significant difference in overall survival (OS) between ET- and CT-treated patients. CT was associated with an increased response rate and toxicity. Therefore, it is recommended that ET be used before CT, except in patients with rapidly progressive disease.

ET resistance (ETR) is a great obstacle in the treatment of HR+/HER2– MBC. Although patients are encouraged to receive three consecutive cycles of ET treatment (8), the clinical benefit rate (CBR) declines rapidly from 70–30% or even lower (9,10). Thus, additional evidence is required in choosing CT or ET in clinical practice.

The purpose of this study was to explore the factors that affect the clinical outcomes of ET and CT in the first-line treatment of patients with ETR HR+/HER2– MBC.

Methods

Patients

In total, 405 consecutive patients with ER+/HER2– MBC treated in the Department of Breast Oncology of Beijing Cancer Hospital (Beijing, China) between June 2013 and June 2015 were retrospectively analyzed. Of these, 135 patients were selected with adjuvant ETR according to the following inclusion criteria: female MBC patients aged ≥18 and ≤75 years with ER+/HER2– primary breast cancer who were administered ET or CT as their first-line treatment. ETR was defined as relapse during adjuvant ET or within 12 months after completing adjuvant ET.

Demographic and clinicopathological data were recorded from electronic medical records. The subsequent maintenance ET followed by first-line CT and the second-line therapy regimen were also recorded. The ethics committee of Beijing Cancer Hospital (Beijing, China) approved this study and written informed consent was obtained from all patients.

ER- and/or progesterone receptor (PR)-positivity was defined as immunohistochemical staining of more than 1% of cells according to current guidelines (11). ER staining of more than 10% of cells was defined as high. Ki-67 index high was defined as >20% positive cells. HER2-negativity was defined as tumors with a HER2 immunohistochemical score of 0 or 1+, or 2+ and FISH negative.

Clinical outcome definitions

RECIST criteria 1.1 was used to assess treatment outcomes (12). The objective response rate (ORR) was defined as the proportion of patients with a complete or partial response (CR + PR/ALL). The CBR was defined as the proportion of patients with a complete or partial response or with stable disease at week 24 (CR + PR + SD ≥24 weeks/ALL). Progression-free survival (PFS) was defined as the interval between commencement of therapy and tumor progression or death. OS was defined as the interval between the commencement of first-line treatment and death from any cause.

Statistical analysis

Demographic and clinicopathological characteristics of patients were grouped as continuous variables and categorical variables. Continuous variables were presented as the median and range. Categorical variables were described as frequency. The baseline characteristics of patients and the response rate between ET and CT were compared using Pearson's χ^2 test or Fisher's exact test. Univariate and multivariate logistic regression analysis were used to explore the factors affecting the ORR of ET *vs.* CT. The Kaplan-Meier method was used to calculate the PFS of ET and CT and the log-rank test was used to compare the PFS of ET and CT. Multivariable Cox proportional hazards regression analysis was used to examine the association of potential influential factors with PFS in first-line treatment. $P \leq 0.05$ was considered statistically significant. The statistical package for the social sciences (SPSS) software version 18.0 was used for the analysis.

Results

Patient characteristics

There were 96 (71.1%) patients that received CT and 39 (28.9%) that received ET as their first-line treatment in the study. Baseline patient characteristics are shown in *Table 1*. Patients in both ET and CT groups had similar clinicopathological characteristics. More patients in the first-line ET group had tumors with invasive lobular cancer and grade I tumors than those in the first-line CT group (P=0.007, P=0.001). However, patients receiving first-line CT had significantly higher frequent visceral metastasis (P=0.001). Among the 39 patients receiving ET, 26 (66.7%) received an aromatase inhibitor (AI), 6 (15.4%) received tamoxifen or toremifene, 3 (7.7%) received fulvestrant, 2 (5.1%) received goserelin and an AI, 1 received only goserelin, and 1 (2.6%) received everolimus and an AI. The most common agent administered to those in the CT group was a taxane (79.2%), followed by capecitabine (43.8%), gemcitabine (36.5%), anthracycline (8.3%), and vinorelbine (6.3%).

Median follow-up was 41.0 months. The ORR to ET was 2.6%, which was significantly lower than that to CT (37.5%) (P<0.001). The median PFS was 12.0 (95% CI, 9.1–15.0) months for the whole population. The median PFS in the ET and CT groups was 11.8 (95% CI, 8.3–15.3) months and 12.0 (95% CI, 7.6–16.4) months, respectively, which was not significantly different (P=0.667) (*Figure 1*, *Table 2*). There were nine deaths until the last follow-up. The median OS of the nine patients was 39.5 (8.4–62.7) months. Therefore, we did not compare OS between the two groups.

To explore factors that affected the ORR, we combined all potential factors into a single factor and used multivariate logistic regression analysis. It showed that bone metastasis and first-line treatment (ET or CT) had significantly affected ORR (14.9% *vs.* 42.6%, P=0.008, OR =0.185; 37.5% *vs.* 2.6%, P=0.025, OR =0.079). In multivariate Cox regression analysis, patients with more than two metastatic sites had a shorter PFS than patients with less than or equal to two metastatic sites, which amounted to 7.5 and 14.5 months, respectively (P=0.031, HR =1.714) (*Figure 2*, *Table 3*).

Then patients with CT were further stratified according to maintenance ET (MET) after CT. Patients on MET had significantly longer PFS (14.3, 95% CI, 14.9–19.7) months than those not on MET (7.5, 95% CI, 5.2–9.9) months, or those on ET as first-line therapy (11.8, 95% CI, 8.3–15.3) months (P=0.003) (*Figure 3*).

Patients receiving CT had more frequent liver and visceral metastasis. In addition, the duration of adjuvant ET less than 2 years indicates primary ET resistance. Therefore, we further analyzed PFS in ET and CT subgroups of liver, visceral metastasis, and duration of adjuvant ET of less or more than 2 years. We found no significant difference of PFS in any of these ET and CT subgroups (*Table 4*).

Discussion

In our study, more than two-thirds of patients with adjuvant ETR received CT in real-world clinical practice. ET is recommended for the patients with ER+/HER2– breast cancer except in cases of rapidly progressive, symptomatic disease, or visceral metastasis at risk of end-organ dysfunction (often termed visceral crisis) (13). Patients with ETR had a greatly decreased CBR with ET, from approximately 70% with first-line therapy to 30% for following lines of therapy. Therefore, ETR is one of the clinical concerns that impacts therapeutic choice. Our finding was also confirmed in a previous report of first-line treatment for patients with MBC in China, in which they showed that HR+ patients who received first-line CT accounted for 97.7% (589/603), while only 1% of patients received ET. That is the reality in China, where a large proportion of ER+/HER2– patients receive CT as first-line treatment.

In our study, more patients with invasive ductal carcinoma, higher histologic grade, liver or visceral metastasis received CT. All these factors were associated with a poor prognosis. However, we found that PFS was not significantly different between patients administered ET and those who received CT (P=0.667). The above factors did not significantly affect the ORR or PFS. The main international guidelines recommend ET as first-line treatment in HR+/HER2– MBC (14,15), which has the same survival benefit with less toxicity and better quality of life compared with CT (14-16). CT is not recommended as first-line therapy for ER+/HER2– breast cancer, even in patients with adjuvant ETR.

Most patients with ET in our study received AIs, which are effective in patients with tamoxifen-resistant MBC as second-line treatment in postmenopausal MBC patients (17). AIs decrease estrogen levels by inhibiting biosynthesis of estrogen (18), which is different from an estrogen receptor modulator (19). In our study, most of the patients who were administered ET (71.8%) received tamoxifen or toremifene in the adjuvant setting. This partly explained the clinical benefit in patients with ETR. Therefore, it is recommended

Table 1 Clinicopathologic characteristics of the metastatic breast cancer patients

Characteristics	ET (n=39) (%)	CT (n=96) (%)	P
Number of patients, n (%)	39 (28.9)	96 (71.1)	
Age [range], year	47 [32–73]	47 [26–69]	0.164
ECOG			0.235
0	31 (79.5)	86 (89.6)	
1			
2	8 (20.5)	10 (10.4)	
Menopause			0.731
Yes	13 (33.3)	35 (36.5)	
No	26 (66.7)	61 (63.5)	
Histology			0.007*
IDC	33 (84.6)	93 (96.9)	
ILC	6 (15.4)	2 (2.1)	
Others		1 (1.0)	
Grade			0.001*
1	6 (15.4)	0	
2	32 (82.1)	91 (94.8)	
3	–	–	
Unknown	1 (2.6)	5 (5.2)	
T			0.057*
T1	23 (59.0)	35 (36.5)	
T2	11 (28.2)	48 (50.0)	
T3	4 (10.3)	9 (9.4)	
T4	0	1 (1.0)	
Unknown	1 (2.6)	3 (3.1)	
LN number			0.403
0	7 (17.9)	25 (26.0)	
1–3	10 (25.6)	28 (29.2)	
≥4	22 (56.4)	42 (43.8)	
Unknown		1 (1.0)	
Estrogen receptor			0.837
Low	10 (25.6)	23 (24.0)	
High	29 (74.4)	73 (76.0)	
Progesterone receptor			0.151*
Negative	2 (5.1)	15 (15.6)	

Table 1 (*continued*)

Table 1 (*continued*)

Characteristics	ET (n=39)	CT (n=96)	P
Positive	37 (94.9)	81 (84.4)	
Ki-67			0.877
≤20%	13 (33.3)	30 (31.3)	
>20%	17 (43.6)	42 (43.8)	
Unknown	9 (23.1)	24 (25.0)	
Adjuvant chemotherapy			0.777*
Yes	35 (89.7)	83 (86.5)	
No	4 (10.3)	13 (13.5)	
Duration of adjuvant hormone therapy			0.838
≤2 years	14 (35.9)	33 (34.4)	
>2 years	25 (64.1)	63 (65.6)	
Adjuvant hormone therapy drug			0.727
TAM or Tore	28 (71.8)	66 (68.8)	
AI	11 (28.2)	30 (31.3)	
Site of metastasis			
Brain metastasis	0	3 (3.1)	0.557*
Bone metastasis	26 (66.7)	48 (50.0)	0.078
Lymph nodes metastasis	17 (43.6)	42 (43.8)	0.986
Soft tissue metastasis	2 (5.1)	14 (14.6)	0.151*
Malignant pleural effusion	2 (5.1)	10 (10.4)	0.508*
Visceral metastasis (liver, lung)	14 (35.9)	64 (66.7)	0.001
Number of sites of metastasis			0.101
1	24 (61.5)	40 (41.7)	
2	7 (17.9)	30 (31.3)	
≥3	8 (20.5)	26 (27.1)	

ET, endocrine therapy; CT, chemotherapy; ECOG, Eastern Cooperative Oncology Group score; TAM, tamoxifen; Tore, toremifene; AI, aromatase inhibitors; *, Fisher exact test.

to consider second- and third-line ET for ER+/HER2– patients who have no urgent need for CT.

Patients who received MET in the CT group had the longest median PFS. Maintenance therapy is recommended for patients who benefit from first-line treatment according to current guidelines. Previous trials have shown that maintenance CT extended the duration of remission (20-23), but improvement in OS was not observed in most trials (24). Nevertheless, toxicity was significantly increased in the maintenance CT arm in most studies. Therefore, MET is a commonly employed strategy aimed at decreasing treatment-related adverse events, without compromising OS in the treatment of ER+/HER2– MBC patients (25).

A multicenter retrospective study involving 314 HER2– MBC patients and 12 cancer centers evaluated the impact of paclitaxel-bevacizumab, maintenance therapy with bevacizumab (BM), and ET in real-world practice. The result from the study confirmed that MET significantly

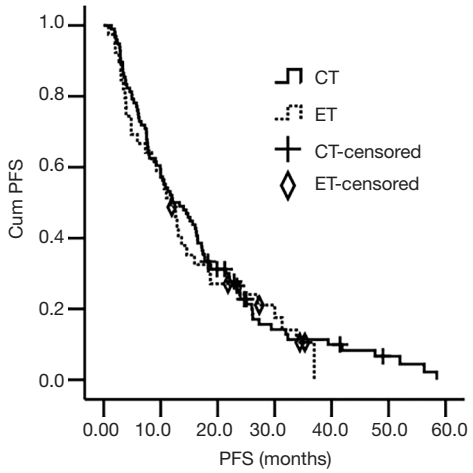

Figure 1 Comparison of cumulative (cum) progression-free survival (PFS) between ER+/HER2– metastatic breast cancer (MBC) patients receiving endocrine therapy (ET) versus chemotherapy (CT) as first-line treatment.

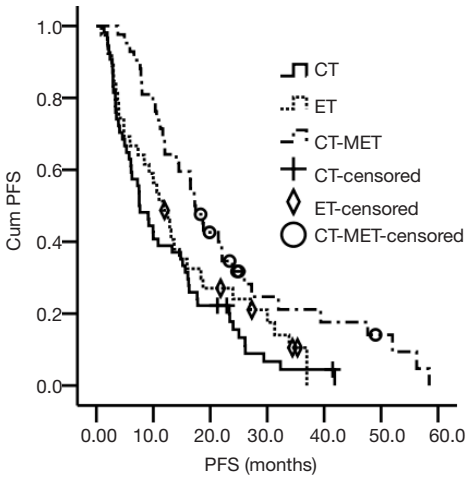

Figure 2 Comparison of cumulative (cum) progression-free survival (PFS) between patients with more than two metastatic sites and less than or equal to two metastatic sites, accounting for 7.5 and 14.5 months, respectively (P=0.031, HR =1.714).

Table 2 Therapeutic effects

Efficacy	ET (n=39)	CT (n=96)	P
Clinical response			
CR, n (%)		1 (1.0)	
PR, n (%)	1 (2.6)	35 (36.5)	
SD, n (%)	30 (76.9)	53 (55.2)	
PD, n (%)	8 (20.5)	7 (7.3)	
ORR, n (%)	1 (2.6)	36 (37.5)	<0.001
CBR, n (%)	31 (79.5)	89 (92.7)	0.036*
PFS (median, 95% CI) (months)	11.8, 8.3–15.3	12.0, 7.6–16.4	0.667

ET, endocrine therapy; CT, chemotherapy; CR, complete response; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CBR, clinical benefit rate; PFS, progression-free survival; *, Fisher's exact test.

improved PFS and OS compared with no maintenance therapies (26). In another study, bevacizumab with or without hormone therapy was used as maintenance therapy after first-line paclitaxel plus bevacizumab in patients with HER2– HR+ MBC. Median PFS in patients who received maintenance bevacizumab with hormone therapy was longer than in those who did not receive hormone therapy (13 and 4.1 months, respectively, P=0.05). Maintenance bevacizumab was also found to be well tolerated (27). Dufresne *et al.* (28) reported that patients benefitted from MET when it was given after first-line CT. MET significantly prolonged PFS from 7.8 to 16.3 months (P<0.0001). There have been two prospective trials exploring the effect of MET (29,30). In one study, patients who received medroxyprogesterone acetate (MPA) as maintenance therapy had longer median time to progression (TTP) (4.9 *vs.* 3.7 months; P=0.02) compared with the control group. However, there was no difference in OS (17.4 *vs.* 18.3 months; P=0.39) between the two groups. In another letrozole-based single-arm phase II study, the median TTP was as long as 18.5 months, and 15.5% of patients had a better response status during letrozole treatment, which was well tolerated and did not significantly affect quality of life. Although these two previous studies suggest a clinical benefit of MET, they each have their own limitations: small sample size, rarely used drug (MPA) in current practice, and a lack of a control arm in the letrozole study. Trédan *et al.* (31) also reported that ER+, HER2– MBC patients with no evidence of progression after first-line taxane + bevacizumab did not achieve longer PFS with maintenance therapy with exemestane + bevacizumab compared with continuation of taxane + bevacizumab in a phase III trial. With these divergent results, it would be too early to draw conclusions regarding the usefulness of MET. Nevertheless, given that MET is well tolerated and improves survival, it might indicate that this treatment strategy should be appropriate

Table 3 The effect of clinicopathological characteristics on ORR and PFS

Characteristics	Category	ORR				PFS			
		ORR (%)	P[a]	P[b]	OR	mPFS (m)	P[a]	P[b]	HR
Age	≤68	25.0	0.528	0.867	1.160	13.1	0.743	0.357	0.713
	>68	29.9				11.2			
Menopause	Yes	25.3	0.458	0.869	0.864	11.0	0.586	0.693	0.905
	No	31.2				12.0			
Grade	G1	0	0.466	0.496	1.375	12.9	0.947	0.465	1.199
	G2	28.7				12.0			
	G3	27.3				8.0			
T	T1	20.7	0.123	0.978	1.019		0.510	0.491	0.845
	T2–3	32.9				10.0			
N	0	31.2	0.389	0.800	0.905	11.0	0.063	0.268	1.177
	1–3	28.9				16.0			
	≥4	23.4				10.0			
ER	Low	27.3	0.984	0.865	0.878	10.0	0.127	0.146	0.685
	High	27.5				12.9			
PR	Negative	29.4	0.843	0.282	2.904	10.6	0.324	0.797	0.904
	Positive	27.1				12.6			
Ki-67	≤20%	23.3	0.419	0.629	1.354	16.5	0.088	0.097	1.464
	>20%	30.5				10.3			
Adjuvant chemotherapy	Yes	25.4	0.180	0.441	1.912	11.7	0.659	0.817	1.082
	No	41.2				17.3			
Duration of adjuvant hormone therapy	≤2 years	24.6	0.527	0.581	1.405	12.9	0.342	0.244	1.302
	>2 years	29.5				11.2			
Brain metastasis	Yes	33.3	0.817	0.657	0.428	16.3	0.892	0.258	0.414
	No	27.3				12.0			
Visceral (liver, lung) metastasis	Yes	35.9	0.012	0.140	3.571	10.8	0.677	0.276	1.365
	No	15.8				13.7			
Bone metastasis	Yes	14.9	0.001	0.008	0.185	10.8	0.083	0.113	1.455
	No	42.6				15.6			
Lymph node metastasis	Yes	30.5	0.477	0.232	0.781	12.0	0.314	0.199	1.217
	No	25.0				12.0			
Number of metastases	≤2 sites	25.5	0.381	0.546	0.552	14.5	0.005	0.031	1.714
	>2 sites	33.3				7.5			
Treatment	CT	37.5	0.003	0.025	0.079	12.0	0.667	0.735	0.898
	ET	2.6				11.8			

[a], single variable analysis P value; [b], multivariate analysis P value. ET, endocrine therapy; CT, chemotherapy; PR, partial response; SD, stable disease; PD, progressive disease; ORR, overall response rate; CBR, clinical benefit rate; PFS, progression-free survival; mPFS, median PFS; HR, hazard ratio.

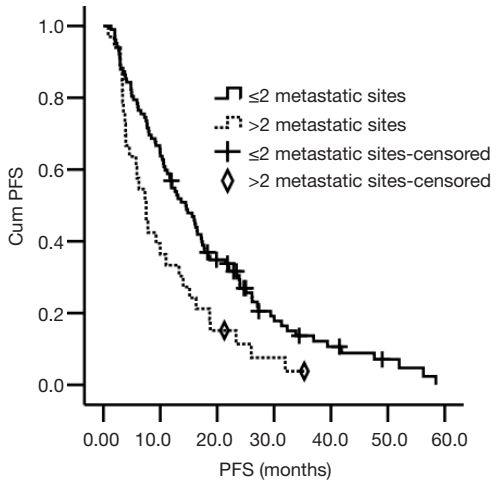

Figure 3 Patients on chemotherapy (CT) were further stratified. Those who received maintenance endocrine therapy (MET) had significantly longer median PFS [14.3 (95% CI, 14.9–19.7) months] compared with those who did not receive MET [7.5 (95% CI, 5.2–9.9) months] or endocrine therapy (ET) as the first-line therapy [11.8 (95% CI, 8.3–15.3) months] (P=0.003).

Table 4 Progression-free survival in the subgroups

Characteristics of patients	CT (n=96)	ET (n=39)	P
Liver metastasis			
No (n=98)	14.5	12.6	0.705
Yes (n=37)	9.2	3.9	0.052
Visceral metastasis			
No (n=57)	10.5	14.6	0.796
Yes (n=78)	13.3	5.9	0.139
Duration of adjuvant hormone therapy			
≤2 years (n=47)	12	12.9	0.637
>2 years (n=88)	12	10	0.248

ET, endocrine therapy; CT, chemotherapy.

for ER+/HER2– MBC patients.

This study had several limitations. First, it was a retrospective analysis in which the baseline between groups was not well balanced. More cases with severe conditions were treated with CT. Second, the baseline quality of life of patients was recorded as an Eastern Cooperative Oncology Group (ECOG) score. However, it was insufficient to reflect the physicians' consideration while making the treatment choice.

In real-world practice, ET and CT are both appropriate treatments for patients with ETR. MET is a good choice for ER+/HER2– patients. Prospective studies are warranted to further compare ET and CT and explore the sequence of these treatments in ETR MBC.

Acknowledgements

We thank Mark Abramovitz, PhD, from Liwen Bianji, Edanz Group China (www.liwenbianji.cn/ac), for editing the English text of a draft of this manuscript.

Funding: General Project of Beijing Natural Science Foundation "Detection and molecular phenotyping of circulating tumor cells in breast cancer based on specific recognition peptide" (item number: 2162044 to Yanlian Yang, execution time: 2016.7–2018.12).

Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The trial was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Peking University Cancer Hospital (2016YJZ33). Written informed consent was obtained from all patients.

References

1. Siegel RL, Miller KD, Jemal A. Cancer Statistics, 2017. CA Cancer J Clin 2017;67:7-30.
2. Kennecke H, Yerushalmi R, Woods R, et al. Metastatic behavior of breast cancer subtypes. J Clin Oncol 2010;28:3271-7.
3. Howlader N, Altekruse SF, Li CI, et al. US incidence of breast cancer subtypes defined by joint hormone receptor and HER2 status. J Natl Cancer Inst 2014;106(5).
4. Lu J, Steeg PS, Price JE, et al. Breast cancer metastasis: challenges and opportunities. Cancer Res 2009;69:4951-3.
5. O'Shaughnessy J. Extending survival with chemotherapy in metastatic breast cancer. Oncologist 2005;10 Suppl 3:20-9.
6. Chung CT, Carlson RW. Goals and objectives in the management of metastatic breast cancer. Oncologist 2003;8:514-20.
7. Wilcken N, Hornbuckle J, Ghersi D. Chemotherapy

alone versus endocrine therapy alone for metastatic breast cancer. Cochrane Database Syst Rev 2003;(2):CD002747.
8. Gradishar WJ, Anderson BO, Balassanian R, et al. Invasive Breast Cancer Version 1.2016, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2016;14:324-54.
9. Chia S, Gradishar W, Mauriac L, et al. Double-blind, randomized placebo controlled trial of fulvestrant compared with exemestane after prior nonsteroidal aromatase inhibitor therapy in postmenopausal women with hormone receptor-positive, advanced breast cancer: results from EFECT. J Clin Oncol 2008;26:1664-70.
10. Ellis MJ, Llombart-Cussac A, Feltl D, et al. Fulvestrant 500 mg Versus Anastrozole 1 mg for the First-Line Treatment of Advanced Breast Cancer: Overall Survival Analysis From the Phase II FIRST Study. J Clin Oncol 2015;33:3781-7.
11. Goldhirsch A, Wood WC, Gelber RD, et al. Meeting highlights: updated international expert consensus on the primary therapy of early breast cancer. J Clin Oncol 2003;21:3357-65.
12. Eisenhauer EA, Therasse P, Bogaerts J, et al. New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). Eur J Cancer 2009;45:228-47.
13. Parnes HL, Cirrincione C, Aisner J, et al. Phase III study of cyclophosphamide, doxorubicin, and fluorouracil (CAF) plus leucovorin versus CAF for metastatic breast cancer: Cancer and Leukemia Group B 9140. J Clin Oncol 2003;21:1819-24.
14. Partridge AH, Rumble RB, Carey LA, et al. Chemotherapy and targeted therapy for women with human epidermal growth factor receptor 2-negative (or unknown) advanced breast cancer: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol 2014;32:3307-29.
15. Cardoso F, Costa A, Norton L, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). Breast 2014;23:489-502.
16. Higgins MJ, Wolff AC. Therapeutic options in the management of metastatic breast cancer. Oncology (Williston Park) 2008;22:614-23; discussion 623, 27-9.
17. Bliss JM, Kilburn LS, Coleman RE, et al. Disease-related outcomes with long-term follow-up: an updated analysis of the intergroup exemestane study. J Clin Oncol 2012;30:709-17.
18. Miller WR. Aromatase inhibitors: mechanism of action and role in the treatment of breast cancer. Semin Oncol 2003;30:3-11.
19. Geisler J. Differences between the non-steroidal aromatase inhibitors anastrozole and letrozole--of clinical importance? Br J Cancer 2011;104:1059-66.
20. Muss HB, Case LD, Richards F 2nd, et al. Interrupted versus continuous chemotherapy in patients with metastatic breast cancer. The Piedmont Oncology Association. N Engl J Med 1991;325:1342-8.
21. Gennari A, Stockler M, Puntoni M, et al. Duration of chemotherapy for metastatic breast cancer: a systematic review and meta-analysis of randomized clinical trials. J Clin Oncol 2011;29:2144-9.
22. Alba E, Martin M, Ramos M, et al. Multicenter randomized trial comparing sequential with concomitant administration of doxorubicin and docetaxel as first-line treatment of metastatic breast cancer: a Spanish Breast Cancer Research Group (GEICAM-9903) phase III study. J Clin Oncol 2004;22:2587-93.
23. Beslija S, Bonneterre J, Burstein H, et al. Second consensus on medical treatment of metastatic breast cancer. Ann Oncol 2007;18:215-25.
24. Park YH, Jung KH, Im SA, et al. Phase III, multicenter, randomized trial of maintenance chemotherapy versus observation in patients with metastatic breast cancer after achieving disease control with six cycles of gemcitabine plus paclitaxel as first-line chemotherapy: KCSG-BR07-02. J Clin Oncol 2013;31:1732-9.
25. Stockler M, Wilcken NR, Ghersi D, et al. Systematic reviews of chemotherapy and endocrine therapy in metastatic breast cancer. Cancer Treat Rev 2000;26:151-68.
26. Gamucci T, Mentuccia L, Natoli C, et al. A Real-World Multicentre Retrospective Study of Paclitaxel-Bevacizumab and Maintenance Therapy as First-Line for HER2-Negative Metastatic Breast Cancer. J Cell Physiol 2017;232:1571-8.
27. Fabi A, Russillo M, Ferretti G, et al. Maintenance bevacizumab beyond first-line paclitaxel plus bevacizumab in patients with Her2-negative hormone receptor-positive metastatic breast cancer: efficacy in combination with hormonal therapy. BMC Cancer 2012;12:482.
28. Dufresne A, Pivot X, Tournigand C, et al. Maintenance hormonal treatment improves progression free survival after a first line chemotherapy in patients with metastatic breast cancer. Int J Med Sci 2008;5:100-5.
29. Kloke O, Klaassen U, Oberhoff C, et al. Maintenance treatment with medroxyprogesterone acetate in patients with advanced breast cancer responding to chemotherapy: results of a randomized trial. Essen Breast Cancer Study Group. Breast Cancer Res Treat 1999;55:51-9.
30. Bertelli G, Garrone O, Bertolotti L, et al. Maintenance

hormone therapy with letrozole after first-line chemotherapy for advanced breast cancer. Oncology 2005;68:364-70.
31. Trédan O, Follana P, Moullet I, et al. A phase III trial of exemestane plus bevacizumab maintenance therapy in patients with metastatic breast cancer after first-line taxane and bevacizumab: a GINECO group study. Ann Oncol 2016;27:1020-9.

Cite this article as: Shao B, Yang Y, Qu J, Li H, Song G, Di L, Jiang H, Yan Y, Wang H, Liu X, Wang J, Kong W. Clinical outcomes with first-line chemotherapy versus endocrine therapy for adjuvant endocrine therapy-resistant metastatic breast cancer. Transl Cancer Res 2018;7(3):676-685. doi: 10.21037/tcr.2018.05.43