RESEARCH ARTICLE

Effect of Hormone Therapy on Long-term Outcomes of Patients with Human Epidermal Growth Factor Receptor 2- and Hormone Receptor-Positive Metastatic Breast Cancer: Real World Experience in China

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Abstract

Background: Among human epidermal growth factor receptor 2 (HER2)-positive breast cancer, more than half are also hormone receptor (HR)-positive. Although HR is a predictive factor for the efficacy of hormone therapy, there are still some uncertainties in regard to the effects on patients with HR-positive and HER2-positive metastatic breast cancers due to the potential resistance to hormone therapy caused by co-expression of HR and HER2. There are no clinical trials directly comparing the efficacy of hormonal therapy with chemotherapy. Materials and Methods: To examine the real-world effect of hormone therapy on patients with HR-positive and HER2-positive metastatic breast cancers, a cross-sectional study of a representative sample of the Chinese population was conducted. The study included 113 patients who received first-line and second-line palliative treatment between 2005 and 2010 in the Cancer Institute and Hospital, Chinese Academy of Medical Science. The effect of hormone therapy on overall survival (OS) was studied. Results: The patients who received hormone therapy (n=51) had better overall survival in contrast to those who received chemotherapy with anti-HER2 therapy (n=62) in first- or second-line treatment. The difference was of borderline statistical significance (51.8m *vs* 31.9m, p=0.065). In addition, the effect of hormone therapy did not differ significantly with other prognostic factors, including age (≤50 years or >50 years), disease free survival (≥2 years or < 2 years) and site of metastasis (visceral or bone/soft tissue). On multivariate analysis, administration of hormone therapy was associated with a trend toward a favorable prognosis (p=0.148, HR=0.693, 95%CI 0.422-1.139). Age more than 50 years was the sole independent harmful prognostic factor (p<0.001, HR=2.797, 95%CI 1.676-4.668). Conclusions: Our data suggest that hormonel therapy may improve outcomes of the patients with ER-positive and HER2-positive metastatic breast cancer.

Keywords: Breast neoplasm - hormonal receptor - human epidermal growth factor receptor-2 chemotherapy

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Introduction

In primary breast cancer, the status of hormonal receptor (HR) including the estrogen receptor (ER) and progesterone receptor (PR) has long been recognized as a prognostic factor (Char-Hong et al., 2014). It is also a predictive factor of the efficacy of hormonal therapy (Goldhirsch et al., 2009). Another fundamental factor, HER-2 is overexpressed or amplified in approximately 15%-25% breast cancer (Slamon et al., 1989; Mohamad et al., 2014). HER-2 status has been confirmed to be a predictive factor of the effect of anti-HER2 therapy. The patients with HER-2 positive breast cancer were usually given the combination of chemotherapy and HER-2 targeted therapy, which could significantly prolong the PFS and OS compared with those receiving chemotherapy alone (Seidman, 2001). It is noteworthy that ER and/or PR is positive in 36%–53 % of the patients with HER2-positive breast cancer (Slamon et al., 2001; Gianni et al., 2010; Hayashi et al., 2013). Nevertheless, there are still some uncertainties regarding to the effect of hormonal therapy on the prognosis of those patients. Firstly, several laboratory studies demonstrated that there was signal cross-talk between HR and HER-2 signal pathway, which may contribute to the resistance to hormonal therapy (Kumar et al., 2002; Chung et al., 2002; Shou et al., 2004). But the results of several clinical trials were inconsistent with the finding above (Elledge et al., 1998; De Laurentiis et al., 2005). On the other hand, hormonal therapy was considered to be the preferred treatment for patients with HR-positive metastatic breast cancer regardless of HER-2 status due to the incurable nature of this disease and its improved toxicity profile. However, recently ASCO guideline suggested the combination of

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chemotherapy and HER-2 targeted therapy be the most appropriate first-line treatment in patients with HER-2 positive and ER-positive advanced breast cancer based on the literature analysis that some first-line chemotherapy trials, such as CLEOPATRA (Swain et al., 2013), did show an OS benefit for chemotherapy and HER2-targeted therapy combination, in which patients with ER-positive breast cancer were also included (Giordano SH et al., 2014) whereas OS superiority was not observed in patients receiving hormonal therapy plus anti-HER2 therapy in both clinical trials (Johnston et al 2009; Kaufman et al., 2009), which compared the combination therapy with hormonal therapy alone.

However, until now, there are no randomized clinical trials directly comparing the effect of hormonal therapy with chemotherapy in metastatic setting due to the difficulties in designing such prospective study. Therefore, it was necessary to determine the status of hormonal therapy on the treatment of these patients. We set out to describe the clinicopathologic features and real-world outcomes of the patients with HR-positive and HER2-positive metastatic breast cancer who received first-line and second-line treatment in Cancer institute and hospital (CIH), Chinese Academy of Medical Sciences(CAMS) between 2005 and 2010. Specifically, we assessed the effect of hormonal therapy in metastatic setting.

Materials and Methods

Patients

All clinical data of this study was collected from the database at Cancer Hospital and Institute, Chinese Academy of Medical Sciences (CAMS). We retrospectively reviewed the data from the patients who had HR-positive/HER2-positive invasive primary breast cancer and metastatic disease diagnosed between 2005 and 2010. The patients with ductal carcinoma in situ or metaplastic carcinoma were excluded.

Pathologic analysis

ER or PR was considered to be positive if ≥1% of the cells had nuclear staining of the receptor on immunohistochemical analysis or if the status had been coded "positive" in the medical records. HR-positive disease was defined, if ER and/or PR was positive. HER2 status was evaluated by immunohistochemical analysis or fluorescence in situ hybridization. HER2 was thought to be positive, if the receptor over-expression staining scores were 3+ on immunohistochemical analysis or the gene copy:CEP-17 ratio was greater than 2.2, which was indicated by gene amplification on fluorescence in situ hybridization.

Statistical methods

OS referred to the period from the date of diagnosis to the date of death or the last follow-up. OS rates were estimated by the Kaplan-Meier method and compared between groups using the log-rank test. Cox proportional hazards models were used to determine the association between the type of treatment and the risk of death after adjustment of disease characteristics. All statistical analyses were done by SPSS 17 software (SPSS Inc., Chicago, IL), and p value less than 0.05 was considered to be statistically significant.

Results

The baseline clinicopathological features and treatment details of these cases were shown in Table 1. The median age was 48 years (range, 24- 84 years). The median follow-up time was 59.9 months (range, 4.1-217.5 months). Sixty-eight patients were dead. The median disease-free survival (DFS) was 27.4 months (range, 1-164.4 months). The median OS was 44.6 months (95%CI:31.7 to 57.7 months) from the date of diagnosis as metastatic disease to the date of the last follow-up.

Of the 113 patients, 61.9% (70/113) had visceral metastasis, and 35.8%(43/113) had merely bone or soft tissue metastasis. Metastatic breast cancer was initially diagnosed in 17.7% (20/113). Of the 72 patients who received first-line chemotherapy, 41.7% (30/72) received taxane-dependent therapy, 27.8% (20/72) received both taxane and anthracycline therapy and 16.7% (12/72) received venorelbine –dependent therapy. Among the 51 patients who received hormonal therapy in first-line treatment or second-line treatment, 15 patients received

Table 1. Patients and their Clinicopathologic Characteristics

Characteristics		N	%
HR status	ER+/PR+	70	61.9
	ER+/PR-	24	21.2
	ER-/PR+	19	16.9
T stage	T1	20	17.7
	T2	36	31.9
	T3	1	0.9
	T4	3	2.7
	N/A	53	46.8
N stage	N0	36	31.9
	N1	23	20.4
	N2	19	16.8
	N3	13	11.5
	N/A	22	19.7
Site of metastasis	Bone/soft tissue	43	38.1
	liver	41	36.3
	Lung	34	30.1
	Brain	8	7.1
Adjuvant treatment			
Adjuvant chemotherapy		80	70.8
Adjuvant hormonal therapy		65	57.5
Adjuvant anti-HER2 therapy		5	4.4
First-line treatment			
Chemotherapy alone		72	63.7
Chemo plus anti-HER2 therapy		27	23.9
Hormonal therapy		14	12.4
Second-line treatment			
Chemotherapy alone		46	47.4
Chemotherapy plus anti-HER2 therapy		14	14.4
Hormonal therapy alone		31	32
Hormonal therapy plus anti-HER2 therapy		6	6.2
Survival status at last followup			
Alive		45	39.8
Dead		68	60.2

*HR, hormonal receptor; ER, estrogen receptor; PR, progesterone receptor

tamoxifen and 36 patients received AIs. Of the 40 patients who received anti-HER-2 therapy, 90% (36/40) administrated trastuzumab in first-line or second-line treatment and 10% (4/40) received lapatinib in second-line treatment.

Assessment of the effect of hormonal therapy in first-line or second-line therapy

Among the 113 patients, 51 patients received hormonal therapy in first-line or second-line therapy and 62 patients received regimen containing chemotherapy with anti-HER2 therapy or not. We found a trend toward better OS in the patients who received hormonal therapy compared to those who did not (51.8m *vs* 31.9m, p=0.065) (Figure 1).

Of the 51 patients receiving hormonal therapy, the proportion of cases who received third-line, fourth-line or fifth-line treatment was 60.1%, 37.3% and 21.6%, respectively. In contrast, the proportion was 56.5%, 37.1% and 24.2% among the 62 patients without hormonal therapy, respectively.

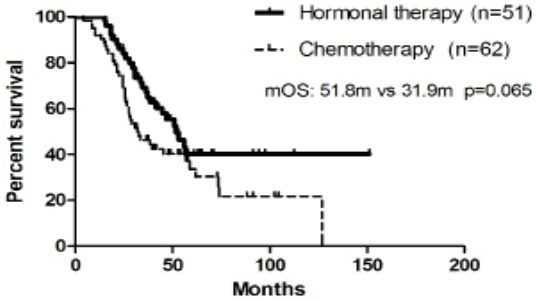

Figure 1. Comparison of the Effects of Hormonal Therapy and Chemotherapy

Table 2. The Log-rank Analysis of OS in Patients who Received Hormonal Therapy or not Stratified by Age, Metastatic Site and DFS

	Hormonal therapy		No hormonal therapy		
	n	mOS (month)	n	mOS (month)	*p*
Age					
≤50 years	31	56.6	33	73.6	0.635
>50 years	20	34.4	29	25.8	0.124
Metastatic site					
Visceral	30	50.6	40	27.6	0.079
Bone/soft tissue	21	NR	22	39.4	0.404
DFS					
≥2 years	21	50.8	26	NR	0.998
<2 years	22	56.6	24	27.6	0.062

DFS, disease-free survival; NR, not reached

Then, the two groups of patients were stratified by the potential prognostic factors including age (≤50 or >50), sites of metastasis (visceral or bone/soft tissue) and DFS (≥2 years or <2 years), and analyzed. The results were summarized in Table 2. There was no significant difference in terms of OS between each subgroups.

Compare of the effect of hormonal therapy and chemotherapy in first-line treatment

Among the 113 patients who received first-line treatment, 14 patients received hormonal therapy, and 99 patients received chemotherapy among which 72 cases accepted chemotherapy alone and 27 patients received both chemotherapy and anti-HER2 therapy. It was demonstrated that the patients who received hormonal therapy had longer overall survival than the chemotherapy arm, but the difference was not significant. (not reached (hormonal) *vs* 41.4m (chemo), p=0.325)

Compare of effect of hormonal therapy and chemotherapy in second-line treatment

Of the 97 patients who received second-line treatment, 37 patients received hormonal therapy, of which 31 patients (83.8%) taken hormonal therapy alone and 6 patients (16.2%) received hormonal therapy plus anti-HER2 therapy, and sixty patients received chemotherapy among which 14 cases (23.3%) taken chemotherapy plus HER2 targeted therapy and 46 cases (76.7%) received chemotherapy alone. As a result, better overall survival was observed in the patients who received hormonal therapy but the difference was not statistically significant(51.8 (hormonal) *vs* 38.4m (chemo), p=0.356).

Assessment of the effect of anti-HER2 therapy in first-line or second-line therapy

Of the 113 patients, 40 patients received anti-HER2 therapy and 73 patients did not. The superiority in overall survival was observed in the patients who received anti-HER2 therapy. However, the difference was not significant (56.6m *vs* 37.0m, p=0.319).

Univariate and multivariate analysis of prognostic factors

We performed univariate and multivariate analysis of the possible prognostic factors on the 113 patients, including treatment and clinicopathological factors. In the

Table 3. Predictors of OS in Univariate and Multivariate Cox Regression Analysis

	Univariant analysis		95%CI		Multivariant analysis		95%CI	
	p	HR	lower	upper	*p*	HR	lower	upper
age)(≤50 *vs* >50)	<0.001	3.109	1.889	5.116	<0.001	2.797	1.676	4.668
Site of metastasis (viseral *vs* bone/ soft tissue)	0.033	0.559	0.328	0.954	0.239	0.718	0.414	1.246
Adjuvant hormonal therapy (yes *vs* no)	0.394	1.05	0.938	1.176				
(Adjuvant HER2 targeted therapy (yes *vs* no)	0.126	1.094	0.975	1.226				
Hormonal therapy in 1st- or 2nd-line treatment (no *vs* yes)	0.067	0.631	0.386	1.034	0.148	0.693	0.422	1.139
HER2 targeted therapy in 1st- or 2nd-line treatment(no *vs* ye)	0.321	0.767	0.454	1.295				
Chemotherapy in 1st-or 2nd-line treatment (no *vs* yes)	0.128	1.493	0.891	2.504				
Third-line treatment (yes *vs* no)	0.161	0.705	0.432	1.15				
Fourth-line treatment (yes *vs* no)	0.333	0.78	0.473	1.289				
Fifth-line treatment (yes *vs* no)	0.286	0.718	0.391	1.319				

univariate analysis, we found that age more than 50 years (p<0.001, HR=3.074, 95%CI 1.902-4.97) and presence of visceral metastasis (p=0.032, HR=0.571, 95%CI 0.342-0.952) were associated with increased risk of death. On the contrary, the use of hormonal therapy in first-line or second-line treatment showed a trend toward reduced risk of death (p=0.067, HR=0.631, 95%CI 0.386-1.034)

Similarly, in the multivariate analysis, the use of hormonal therapy showed a trend toward reduced risk of death (p=0.148, HR=0.693, 95%CI 0.422-1.139). Age (more than 50 years) was the sole independent harmful prognostic factor in terms of OS (p<0.001, HR=2.797, 95%CI 1.676-4.668.) (Table 3).

Discussion

Our results indicated that hormonal therapy may provide greater survival benefits to the patients with HR-positive and HER2-positive breast cancer than cytotoxic agents in metastatic setting. In clinical practice, hormonal therapy and chemotherapy were frequently considered for the patients with HR-positive and HER2-positive metastatic breast cancer. In metastatic setting, hormonal therapy was considered to be the preferred choice for the patients with HR-positive breast cancer in the absence of symptomatic visceral metastasis due to the improved toxicity profiles, higher quality of life and less expense compared to chemotherapy. But we still need to confirm its effect in this specific group of patients because of the more aggressive nature of HER-2 positive disease and the greater chance of developing resistance to hormonal therapy which was caused by the co-expression of HER2 and HR. Our data suggested that hormonal therapy was appropriate for the patients with HR-positive and HER-2 positive metastatic breast cancer.

It was also indicated that that any cross-talk that occurred between ER and HER2 was insufficient to degrade the effect of hormonal therapy to the patients with ER-positive and HER2-positive breast cancer. It has been asserted that the cross-talk between ER and HER2 is bidirectional and may cause resistance to tamoxifen and AIs. Dowssett et al. (Dowsett et al., 2006) found no survival benefits of tamoxifen addition in the adjuvant treatment settings in the patients with HR-positive and HER-2-positive breast cancer. However, as they noted, the sample size was relatively small (n=75) and duration of tamoxifen administration was only 2 years. Furthermore, that study used a unique definition of HR status (H-score), making it difficult to compare with others. In 2005, a meta analysis showed a higher risk of disease-progression within 6 months in the patients who had HER-2-positive metastatic breast cancer and received hormonal therapy compared to those with HER-2-negative disease (HR=1.42, 95%CI 1.32-1.52, p<0.001). Nevertheless, some studies in the meta analysis used nonstandard methods like PCR, Southern-blot or ELISA to determine HER-2 status (De Laurentiis et al., 2005). Therefore, our results provided a different perspective in this area.

In contrast, in the study of Elledge et al. (Elledge RM et al., 1998), there was no significant difference in the efficacy of tamoxifen between the patients with HR positive and HER-2 positive metastatic breast cancer, including objective response rate, PFS and OS. Also, not in a metastatic setting but a adjuvant setting, Naoki Hayashi et al. (2013) found significant improvement of DFS in 128 patients with ER-positive and HER-2 positive breast cancer who received hormonal therapy after chemotherapy and trastuzumab compared to 46 patients who merely received chemotherapy and trastuzumab and a similar trend toward overall survival. Taken these findings together, it was suggested that hormonal therapy was beneficial regardless of the extent of disease.

There were also some limitations in the study. First, the sample size was relatively small, making it difficult to determine the probable subgroup of patients who may obtain greater benefits from hormonal therapy. Second, the association between quantitative expression levels of ER or PR and prognosis was not assessed, since the quantitative expression levels of some patients in the study were not available in the medical records.

In summary, our findings demonstrated that hormonal therapy may improve outcomes of the patients with ER-positive and HER2-positive metastatic breast cancer, as was significant in directing clinical practice.

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