

## Effective Hormone Therapy Reduces the Efficacy of Subsequent Chemotherapy in Hormone-Receptor-Positive Metastatic Breast Cancer

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Received date: July 04, 2016; Accepted date: July 21, 2016; Published date: July 27, 2016

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### Abstract

**Objective:** Hormone Therapy (HT) is usually introduced to patients with hormone-receptor-positive metastatic breast cancer without life-threatening metastasis prior to chemotherapy. Many physicians expect HT not to affect the efficacy of subsequent chemotherapy, but there is no evidence to confirm this. In this retrospective study, we investigated the efficacy of chemotherapy after hormone therapy for metastatic breast cancer.

**Methods:** Patients who received chemotherapy after hormone therapy for metastatic breast cancer between 2004 and 2014 at our institution were reviewed, and the efficacy of HT and the efficacy of subsequent chemotherapy were evaluated based on the tumor response and the duration of the therapy. If multiple-line therapies were introduced, the efficacies were evaluated by the best response, longest duration among therapies, and total duration of therapies, and we analyzed the relationship between the efficacies of HTs and chemotherapies.

**Results:** Twenty-nine patients were eligible. The median patient age was 60 years old. The major metastatic sites included bone (17 patients), the lungs (10 patients), and lymph nodes (10 patients). The clinical benefit (CB) rate of all HTs was 62% and the patients received HTs for a median of 20.4 months. Meanwhile, the CB rate of all chemotherapies was 79%, and the patients received chemotherapies for a median of 24.8 months. The CB rates, the longest durations, and the total durations of prior HTs were not associated with the efficacy of subsequent chemotherapy. However, the total duration of the chemotherapies in the patients with very effective HTs (total duration of HTs > 20 months, longest duration of HT > 14 months, and HTs with CBs) was significantly shorter than for the others (MST 13.1 m vs. 26.8 m;  $p=0.035$ ).

**Conclusions:** These results suggest that the efficacy of chemotherapies was reduced after very effective HTs.

**Keywords:** Secondary breast neoplasms; Chemotherapy; Hormone therapy; Cross-resistance

### Introduction

According to the guidelines for metastatic breast cancer, such as Hortobagyi's algorithm and the NCCN guidelines, hormone therapy (HT) should be introduced in cases of hormone-receptor (HR)-positive metastatic breast cancer prior to chemotherapy if the metastatic tumor is not life-threatening because the adverse effect of hormone therapy is mild [1,2] and, finally, the patients require chemotherapy if the metastatic tumor is going to threaten their life. This strategy is based on the hypothesis that hormone therapy does not affect the efficacy of subsequent chemotherapy. However, there is no evidence to confirm this. Moreover, the mechanism of HT does not simply involve antagonizing estrogen, and HT may have a similar mechanism to chemotherapy or molecular-targeted therapy [3].

Second-line chemotherapy is often not as effective as first-line chemotherapy, even if the second-line agents have a different mode of action from the first-line ones. This phenomenon is often explained by cross-resistance between the drugs [4].

Considering this background, there may be cross-resistance between HT and chemotherapy, so we retrospectively investigated the efficacy of chemotherapy after HT to resolve this issue.

### Patients and Methods

The records of breast cancer patients who had received chemotherapy after HT for locally advanced or metastatic breast cancer at Gifu University Hospital between 2004 and 2014 were reviewed. The therapy in each case was investigated, and the efficacy of HT and chemotherapy was evaluated in terms of the objective response and the duration of the therapies.

The objective response to treatment was categorized into four groups: complete response (CR), partial response (PR), stable disease (SD), and progressive disease (PD). CR indicates that the target lesion clinically disappeared, PR indicates that the target lesion was clinically reduced in size after treatment and SD indicates that the size of the target lesion appeared not to change, with stable disease lasting for more than six months being defined as "long SD." Meanwhile, PD indicates that the target lesion has increased in size. This categorization was determined based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, although these criteria were not rigorously applied in this study.

If the patients received multi-line therapies, the efficacy of the therapies in each patient was evaluated using best response among the therapies, the longest duration among the therapies, and total duration of the therapies.

When we analyzed the efficacy of overall HTs and overall chemotherapies, we calculated the clinical benefit (CB, defined as CR +PR+long SD) rate of HTs, the median of the longest duration of HTs, and the median survival time (MST) according to the Kaplan-Meier curve of the total duration of HTs and chemotherapies.

The CB rates were compared using the chi-square test. The total durations of the therapies were compared by the log-rank test.

This study was approved by the ethical committee of Gifu University, Graduate School of Medicine.

## Results

### Patient characteristics

A total of 29 patients received chemotherapy after HT for locally advanced or metastatic breast cancer. The median age of these patients was 60 years old. Most of the primary tumours exhibited a size of 2-5 cm (T2). Twenty-one patients had an N (+) status, while twenty-three patients had estrogen-receptor (ER)-positive tumor, and four patients had HER2-positive tumors. The metastatic sites included the bones (17 patients), lungs (10 patients), liver (4 patients), lymph nodes (10 patients), and other organs (11 patients). HR status in six patients was unknown and HER2 status in eleven patients was unknown because they had not been examined. The details are shown in Table 1.

	No.
Age (years)	
<49	3
50-59	10
≥ 60	16
Menopausal status	
Premenopausal	3
Postmenopausal	26
T factor	
T1	5
T2	9
T3	3
T4	7
Unknown	5
Nodal status	
N(-)	4
N(+)	21
Unknown	4
HER2 status	

(-)	14
(+)	4
Unknown	11
Hormone receptors status	
ER(+)/PR(+)	17
ER(+)/PR(-)	6
ER(-)/PR(+)	0
Unknown	6
Metastatic sites	
Bone	17
Lung	10
Liver	4
Lymph node	10
Other	11

**Table 1:** The patients' characteristics (n=29).

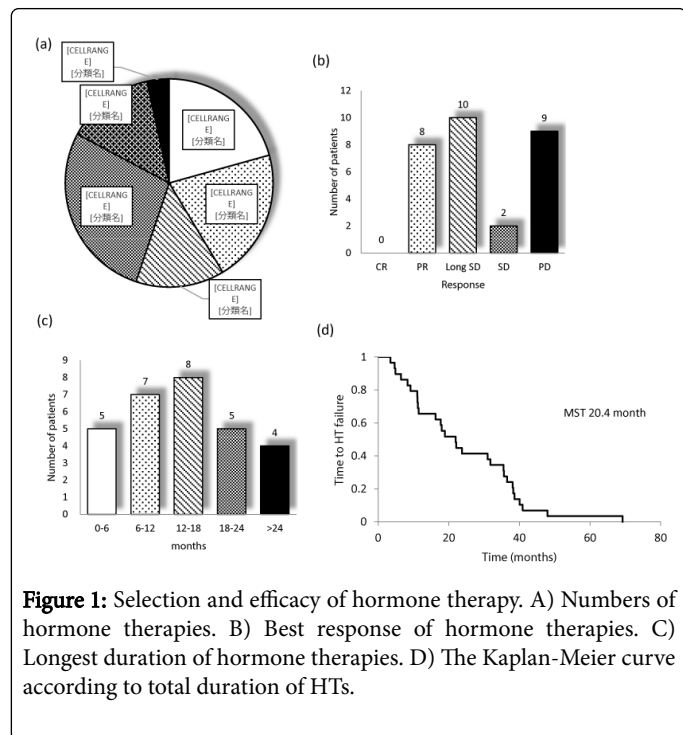
	No.
Prior hormonal therapy	
Exemestane	13
Anastrozole	10
Letrozole	14
High-dose toremifene	14
Tamoxifen	3
Fulvestrant	9
LHRH analogue	12
Subsequent chemotherapy	
Anthracycline	2
Taxane	5
Oral fluoropyrimidine	20
Vinorelbine	2
Trastuzumab	3

**Table 2:** The selection of hormone therapy and subsequent chemotherapy.

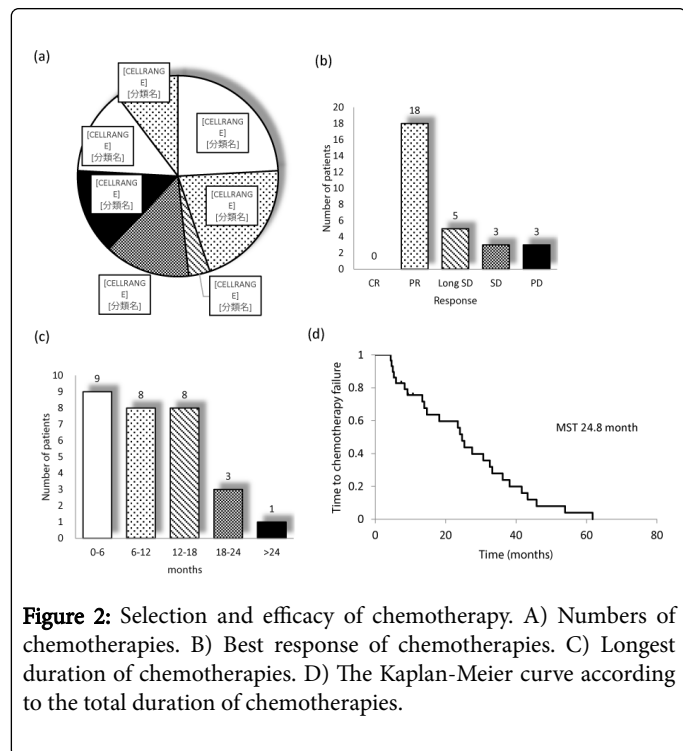
### Selection and efficacy of hormone therapy and chemotherapy

The patients received an average of 3.03 lines of hormone therapy after recurrence (Figure 1a). Non-steroidal aromatase inhibitors (AIs) were administered to 31 cases, steroidal AIs were administered to 24 cases, and selective estrogen receptor modulators (SERMs) were administered to 29 cases. The details are shown in Table 2. The hormone therapies produced 8 cases of PR, 10 cases of long SD, 2 cases

of SD, and 21 cases of PD, with a CB rate of 62.0% (Figure 1B). The median of the longest duration of HTs was 14.2 (2.3-4.3) months (Figure 1C). MST of HTs was 20.4 months (Figure 1D).



**Figure 1:** Selection and efficacy of hormone therapy. A) Numbers of hormone therapies. B) Best response of hormone therapies. C) Longest duration of hormone therapies. D) The Kaplan-Meier curve according to total duration of HTs.



**Figure 2:** Selection and efficacy of chemotherapy. A) Numbers of chemotherapies. B) Best response of chemotherapies. C) Longest duration of chemotherapies. D) The Kaplan-Meier curve according to the total duration of chemotherapies.

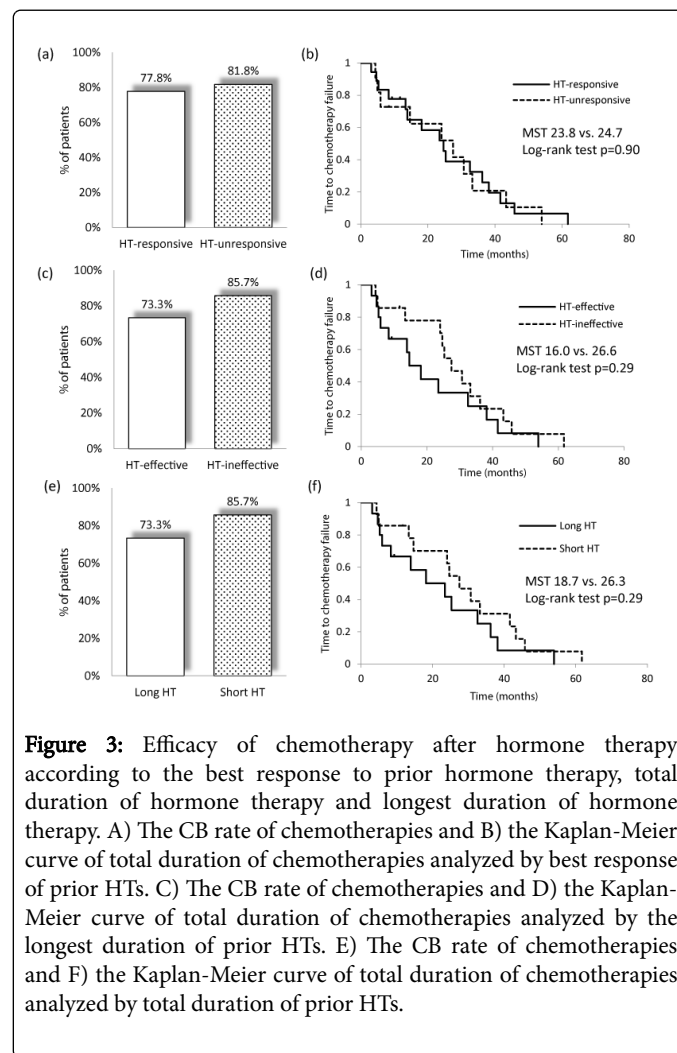
Meanwhile, the patients received an average of 3.69 lines of chemotherapy after HT (Figure 2A). After HT, oral 5-FU derivatives were administered to 41 cases, taxanes were administered to 31 cases, and anthracyclines were administered to 5 cases. Patients with a HER2-positive status also received trastuzumab. The chemotherapies

produced 18 cases of PR, 5 cases of long SD, 3 cases of SD, and 3 cases of PD (Figure 2B), with a CB rate of 79.3%. The median of the longest duration of chemotherapies was 9.3 (1.6-24.7) months (Figure 2C). MST of chemotherapies was 24.8 months (Figure 2D).

### Efficacy of chemotherapy analyzed by the response to prior hormone therapy

We analyzed the efficacy of the chemotherapy based on the response to prior HTs. HT was considered to be effective if the HT regimen produced at least one CB through all HT regimens.

The numbers of HT-responsive and -unresponsive cases were 18 and 11, respectively. The CB rate of chemotherapies was 77.8% (PR: 10, long SD: 4, SD: 2, PD: 2) among the HT-responsive cases, while it was 81.8% (PR: 8, long SD: 1, SD: 1, PD: 1) among the HT-unresponsive ones (Figure 3A); these differences were not significant ( $p=0.79$ ). MSTs of chemotherapies among the HT-responsive and -unresponsive cases were 23.8 and 24.7 months, respectively, which were not significantly different ( $p=0.90$ ) (Figure 3B).



**Figure 3:** Efficacy of chemotherapy after hormone therapy according to the best response to prior hormone therapy, total duration of hormone therapy and longest duration of hormone therapy. A) The CB rate of chemotherapies and B) the Kaplan-Meier curve of total duration of chemotherapies analyzed by best response of prior HTs. C) The CB rate of chemotherapies and D) the Kaplan-Meier curve of total duration of chemotherapies analyzed by the longest duration of prior HTs. E) The CB rate of chemotherapies and F) the Kaplan-Meier curve of total duration of chemotherapies analyzed by total duration of prior HTs.

### Efficacy of chemotherapy analyzed by the longest duration of prior HT

The analysis of the efficacy of chemotherapy based on the longest duration among HTs was as follows. HT was considered to be effective if the longest duration among HTs was longer than 14 months, which is the median of the longest duration of HTs among all patients.

The numbers of HT-effective and -ineffective cases were 15 and 14, respectively. The CB rate of chemotherapies was 73.3% (PR: 9, long SD: 2, SD: 1, PD: 3) among the HT-effective cases, while it was 85.7% (PR: 9, long SD: 3, SD: 2, PD: 0) among the HT-ineffective cases (Figure 3C); these differences were not significant ( $p=0.41$ ). The MSTs of chemotherapies among the HT-effective and -ineffective cases were 16.6 and 26.6 months, respectively, which were not significantly different ( $p=0.29$ ) (Figure 3D).

### Efficacy of chemotherapy analyzed by the total duration of prior hormone therapy

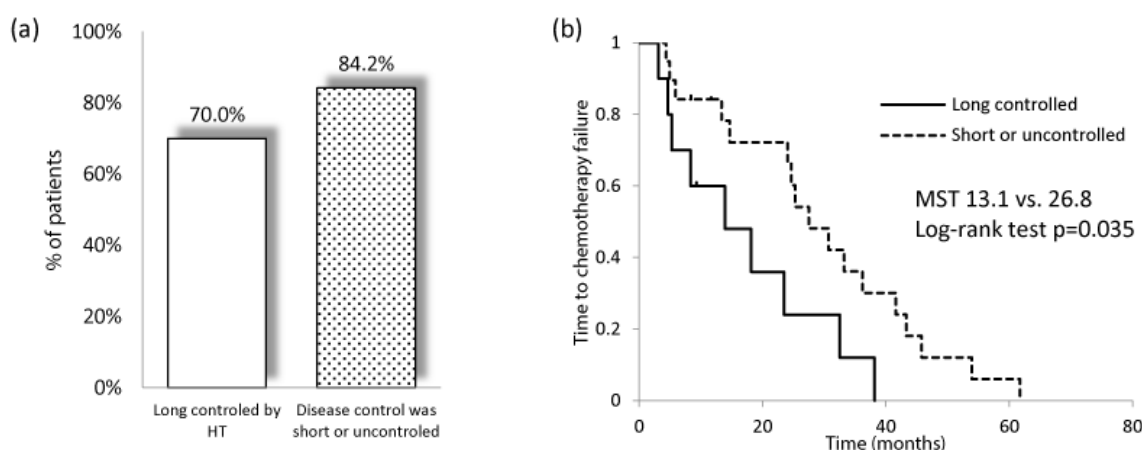
The analysis of the efficacy of chemotherapy based on the total duration of prior HTs was as follows. The HT was considered to be effective if the total duration of HTs was longer than 20 months, which is the MST of prior HT among all patients.

The numbers of HT-effective and ineffective cases were 15 and 14, respectively. The CB rate of chemotherapies was 73.3% (PR: 8, long SD: 3, SD: 1, PD: 3) among the HT-effective cases, while the CB rate was 85.7% (PR: 10, long SD: 2, SD: 2, PD: 0) among the HT-ineffective ones (Figure 3E); these differences were not significant ( $p=0.41$ ). The MSTs of chemotherapies among the HT-effective and -ineffective cases were 18.7 and 26.3 months, respectively, which were not significantly different ( $p=0.29$ ) (Figure 3F).

### Efficacy of chemotherapy among the patients with very effective HT

The patients with CB of HT, longest duration of HT more than 14 months, and total duration of HT more than 20 months were less sensitive to chemotherapy.

The number of such patients was 10 and the CB rate of chemotherapies was 70.0% (PR: 6, long SD: 1, SD: 1, PD: 2) among them, while the CB rate was 84.2% (PR: 12, long SD: 4, SD: 2, PD: 1) among the other 19 patients (Figure 4A); these differences were not significant ( $p=0.37$ ). The MSTs of the chemotherapies among the HT-very effective cases and others were 13.1 and 26.8 months, respectively; this difference was statistically significant ( $p=0.035$ ) (Figure 4B).



**Figure 4:** Efficacy of chemotherapy in cases that could receive clinical benefit of HT, total duration of HT more than 20 months, and longest duration of HT more than 14 months. A) The CB rate of chemotherapies and B) the Kaplan-Meier curve of total duration of chemotherapies in cases with long controlled disease and cases with short or uncontrolled disease by HTs.

## Discussion

We evaluated the efficacy of chemotherapy after HT for metastatic breast cancer and found ineffectiveness of chemotherapy after effective HT. In particular, the patients with both good response of HT and long duration of HT did not benefit from subsequent chemotherapy compared with the other patients.

For patients who have been previously exposed to drug therapies, a drug with a different mechanism of action from prior drugs may provide clinical benefit [5,6]. However, the duration of later therapies has been shown to decrease [7] and eventually all agents become ineffective. This suggests that there is cross-resistance between drugs with different mechanisms of action.

Estrogen has been considered to play an important role in the progression of HR-positive breast cancer, and the speculated mechanism of hormone therapy for breast cancer is blocking signaling through estrogen receptor (ER), which promotes cell proliferation [8], and many physicians may expect hormone therapy not to affect the efficacy of subsequent chemotherapy. However, the mechanism of most chemotherapy agents also involves blocking intracellular proliferation signaling like hormone therapy agents. In particular, targeted therapy agents such as bevacizumab and trastuzumab seem to have similar mechanisms of action to hormone therapy agents, which suggests that prior hormone therapy also affects the efficacy of subsequent chemotherapy.

Another possible rationale behind the ineffectiveness of chemotherapy after effective HT is that HT-effective HR-positive

breast cancer may naturally be resistant to chemotherapy. On the basis of this hypothesis, some trials have been established to investigate the efficacy of adjuvant or neoadjuvant chemotherapy based on the response to prior neoadjuvant HT, such as the Z1031B trial and the NEOS trial [9,10]. However, the results of the Z1031B trial failed to prove such a hypothesis (the NEOS trial is ongoing). These results may support our findings.

In conclusion, we found that effective HT for metastatic breast cancer may affect the efficacy of subsequent chemotherapy, which should be taken into consideration when we need to change the therapy for HR-positive metastatic breast cancer after disease progression.

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