The efficacy of second-line hormone therapy for recurrence during adjuvant hormone therapy for breast cancer

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Ther Adv Med Oncol

2014, Vol. 6(2) 36–42

DOI: 10.1177/

1758834013517734

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Abstract

Objectives: The recurrence of breast cancer during adjuvant hormone therapy is often targeted by second-line hormone therapy. However, there has been a lack of prior success with such treatments. We retrospectively investigated the efficacy of subsequent hormone therapy.

Methods: Patients who underwent breast cancer surgery between 2006 and 2012 at our institution were investigated.

Results: A total of 20 patients developed recurrence during adjuvant hormone therapy. There were four patients with luminal A, seven with luminal B and six with luminal HER2 tumors, respectively. Twelve patients received subsequent hormone therapy, and eight patients received chemotherapy. Subsequent hormone therapy produced one partial response (PR), two long stable disease (SD), one SD and five progressive disease (PD). A clinical benefit (CB) was obtained by 33%. Subsequent chemotherapy produced one complete response (CR), two PRs, one long SD and two PD, resulting in a CB in 66%. Among those who received any hormone therapy, the best responses were two PR, three long SD and one SD. A CB was obtained by 38%, while seven patients did not have any CB from hormone therapy. Meanwhile, the best responses to chemotherapy were two CRs, four PRs, three SD and two PD, thus resulting in a CB in 72%. All luminal A cases obtained a long SD or SD with hormone therapy. However, the CB of hormone therapy for non-luminal A cases was only 30%.

Conclusions: The efficacy of hormone therapy for recurrence during adjuvant hormone therapy is poor, and when selecting therapy for such patients, the breast cancer subtype should be taken into account.

Keywords: breast neoplasms, drug resistance, hormone

Introduction

Most patients with hormone-receptor (HR)-positive early breast cancer benefit from adjuvant hormone therapy [Cutter *et al.* 2011]. Unfortunately, recurrence develops in some cases during adjuvant hormone therapy. According to Hortobagyi's algorithm and the National Comprehensive Cancer Network (NCCN) guidelines, such patients are eligible for second-line hormone therapy [Hortobagyi, 2011; NCCN, 2013]. However, the efficacy of the subsequent hormone therapy is uncertain because of the lack of prior success with such

treatment, and chemotherapy may be a better choice for such patients.

Hormone resistance in breast cancer can be classified into two categories: primary resistance (*de novo* resistance) and secondary resistance (acquired resistance). Breast cancer with primary resistance is naturally not sensitive to hormone therapy, even though it is HR positive. Breast cancer with secondary resistance has acquired hormone resistance after previously being sensitive to hormone therapy, and another type of hormone therapy may still be effective [Johnston, 2010].

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Although this classification of cancers is useful, it is often difficult to distinguish them in the clinical setting, especially in the adjuvant setting because of the lack of measurable lesions after surgery.

Recently, some clinical research studies about overcoming hormone resistance were reported. The BOLERO-2 trial examined the effects of the addition of everolimus, an mTOR inhibitor, to exemestane in patients with HR-positive advanced breast cancer [Baselga *et al.* 2012]. In this study, primary resistance was defined as less than 24 months of efficacy from endocrine therapy before recurrence in the adjuvant setting. Similarly, the TAMRAD trial, which examined the effects of the addition of everolimus to tamoxifen, defined the patients with primary resistance as those relapsing during or within 6 months of stopping adjuvant hormone therapy [Bachelot *et al.* 2012]. In these trials, primary resistance was defined according to the interval between the start of the adjuvant therapy and the diagnosis of recurrence. However, the true nature of the resistance in these studies was not clear.

To elucidate whether subsequent hormone therapy for patients with recurrence during adjuvant hormone therapy is effective, and which of hormone therapy or chemotherapy is better for such patients, we retrospectively investigated the cases of recurrence during adjuvant hormone therapy in our institution, and explored the efficacy of subsequent hormone therapy in comparison with the efficacy of cytotoxic chemotherapy.

Patients and methods

The records of breast cancer patients who underwent surgery for breast cancer at the Gifu Prefectural General Medical Center between 2006 and 2012 were reviewed. The patients with recurrence during adjuvant hormone therapy were selected, and their data were investigated. The therapies which the patients received were investigated, and the efficacy of subsequent hormone therapy and cytotoxic chemotherapy was evaluated from the viewpoint of the objective response and time to treatment failure (TTF).

In our study, patients were divided into three breast cancer subtypes; luminal A (defined as HR-positive, HER2-negative, low nuclear grade), luminal B (defined as HR-positive,

HER2-negative, intermediate or high nuclear grade) and luminal HER2 (defined as HR-positive, HER2-positive, any nuclear grade). Because Ki67 was not investigated in most cases, luminal A and luminal B cases were divided by the 'nuclear grade'. The nuclear grade is the tumor grading system used in Japan, which consists of a nuclear atypia score and mitotic counts score. Nuclear atypia is given a score of 1–3 (score 1: regular uniform cells; score 2: moderate nuclear size and variation; score 3: marked nuclear variation). Mitotic counts are also given a score of 1–3 (score 1: 0–5 mitoses/10 high-power fields (hpf); score 2: 5–10 mitoses/10 hpf; score 3: ≥ 10 mitoses/10 hpf). The nuclear grade is then given one of three grades based on the sum of these two items (low grade: 2–3; intermediate grade: 4; high grade: 5–6).

The efficacy of the treatment was categorized into four categories: complete response (CR), partial response (PR), stable disease (SD) and progressive disease (PD). A CR means that the target lesion clinically disappeared. A PR indicates that the target lesion clinically shrunk after treatment. SD means that the size of the target lesion appears to be the same as before, and stable disease status lasting more than 6 months was defined as long SD. PD means that the target lesion has increased in size. This categorization is based on the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, but these criteria were not rigorously applied to our study. A clinical benefit (CB) was defined as CR + PR + long SD.

Our retrospective study met ethical guidelines, including adherence to the legal requirements of our country.

Results

Patient characteristics

A total of 534 women underwent surgery for breast cancer. Among them, 20 developed recurrences during adjuvant hormone therapy. The median age of these patients was 62 years. The median tumor size was 30 mm. The nodal status was N(–) in five patients and N(+) in 15 patients. Seven patients were HER2 positive. The metastatic sites were the bones (two patients), lungs (four patients), liver (five patients), lymph nodes (seven patients) and other organs (four patients). The distribution of tumor subtypes was 20%

Table 1. The patients' characteristics.

	N
Age (years)	
< 49	4
50–59	4
≥ 60	12
Menopausal status	
Premenopausal	4
Postmenopausal	16
Tumor size (mm)	
≤ 20	4
20–50	11
> 50	5
Nodal status	
N(–)	5
N(1–3)	7
N(≥4)	8
Nuclear grade	
1	5
2	5
3	8
HER2 status	
(–)	13
(+)	7
Hormone receptor status	
ER(+)/PR(+)	10
ER(+)/PR(–)	10
ER(–)/PR(+)	0
Metastatic sites	
Bone	2
Lung	4
Liver	5
Lymph node	7
Other	4
Subtypes	
Luminal A	4
Luminal B	8
Luminal HER2	6

(4/20), 35% (7/20) and 30% (6/20) for luminal A, luminal B and luminal HER2, respectively. Two patients' subtypes were unknown. The details are shown in Table 1.

The selection of subsequent therapies

All four patients with the luminal A subtype received subsequent hormone therapy, and the patients with other subtypes received either hormone therapy or chemotherapy (Figure 1A). The

patients with lymph node, liver and bone metastases more often received hormone therapy than chemotherapy. Meanwhile, the patients with lung metastases more often received chemotherapy than hormone therapy (Figure 1B). In our study, the patients with a longer interval between the start of the adjuvant hormone therapy and recurrence were more likely to receive chemotherapy (Figure 1C).

The efficacy of subsequent therapy

The subsequent hormone therapy produced one PR, two long SD, one SD and five cases of PD. The CB (CR + PR + long SD) of the second-line hormone therapy was 33% (3/9). The subsequent chemotherapy produced one CR, two PRs, one long SD and two PDs. The CB of the chemotherapy was 66% (4/6) (Figure 2A). The efficacy of hormone therapy for three cases with lymph node metastases was unable to be evaluated because another therapy, such as radiation or surgical resection, was used in combination with the hormone therapy. Two patients treated with chemotherapy dropped out of their treatment because of its adverse effects. All luminal A cases received hormone therapy, and they all obtained either a long SD or SD. However, in most luminal B and luminal HER2 cases, hormone therapy did not have any CB (PD: 4/5) (Figure 2B). All patients with bone metastasis obtained a CB from hormone therapy. Both of the PD cases treated with chemotherapy had lymph node metastases (Figure 2C). We could not statistically compare the TTF of hormone therapy and chemotherapy because of the small number of patients. However, the TTF of hormone therapy seemed to be shorter than that of chemotherapy (Figure 2D).

The best response to all therapies

We also investigated the best response to hormone therapy or chemotherapy through all-line therapies after recurrence. Among the patients receiving multiple hormone therapies, the best responses were two PR, three long SD and one SD. Seven patients did not receive any CB from hormone therapy. The CB rate in this setting was therefore 38% (5/13). Meanwhile, multiple-line chemotherapies produced two CRs, four PRs, two long SDs, one SD and two cases of PD. The CB of multiple chemotherapies was 72% (8/11) (Figure 3A).

Figure 1. The selection of the therapies after recurrence. (a) The selection of the therapy based on the breast cancer subtype. (b) The selection of the therapies based on the metastatic sites. (c) The relationship between the interval before recurrence and the selection of the subsequent therapy. ANA, anastrozole; LET, letrozole; TAM+LHRH, tamoxifen+ LHRH analogue.

All luminal A cases received only hormone therapy, and they all had a long SD or SD response. The best overall responses to hormone therapy for luminal B and luminal HER cases were two PRs, one long SD and seven cases of PD (Figure 3B). The CB of hormone therapy for luminal A cases was 67% (2/3). Meanwhile, the CB of hormone therapy and chemotherapy for non-luminal A was 30% (3/10) and 67% (6/9), respectively (Figure 3C).

Discussion

The patients who developed recurrence during adjuvant hormone therapy had a poor response to subsequent hormone therapy. In our study, the CB of subsequent hormone therapies was 38%. In other words, 62% of the patients did not receive any benefit from the subsequent hormone

therapies. Meanwhile, 72% of patients benefited from subsequent chemotherapies.

Although the NCCN recommends second-line hormone therapy for patients who progress within 12 months of completing adjuvant hormone therapy, our results suggested that the efficacy of subsequent hormone therapy after recurrence during adjuvant hormone therapy was worse than that of the so-called second-line hormone therapy.

Thürlimann and colleagues [Thürlimann *et al.* 2004] reported that when tamoxifen was used as the second-line hormone therapy after anastrozole, it produced a CB in 50% of cases, and anastrozole after tamoxifen produced a CB in 44% of cases. Iaffaioli and colleagues [Iaffaioli *et al.* 2005] reported that exemestane as the second-line hormone therapy after anastrozole

Figure 2. The efficacy of subsequent therapy for recurrence during adjuvant therapy. (a) The overall response to the hormone therapy and chemotherapy. (b) The response to the therapies based on the breast cancer subtypes. (c) The clinical benefit rate and progressive disease rate analyzed by metastatic sites. (d) The time to treatment failure of hormone therapy and chemotherapy.

produced a CB in 44% of cases. In this report, the HR status in 19% of the patients was not investigated. Chia and colleagues [Chia *et al.* 2008] reported that exemestane after a nonsteroidal aromatase inhibitor (AI) produced a CB in 32.2% of cases, and fulvestrant (250 mg) after a nonsteroidal AI produced a CB in 31.5% of cases. In this trial, 58.7% of the patients had received two or more previous therapies. Since our study is a retrospective and small trial, we cannot simply compare our results with the other trials. However, our outcomes seemed to be worse than those of the other studies, suggesting that subsequent hormone therapy for recurrence during adjuvant hormone therapy is less effective than the so-called second-line hormone therapy.

When the breast cancer subtypes are considered, the patients with luminal A cancers had a

good response to hormone therapy, even when it was targeted for recurrence during adjuvant hormone therapy. However, the luminal B and luminal HER2 cases had a poor response to subsequent hormone therapy. Therefore, when selecting the subsequent therapy in this setting, the breast cancer subtype should be taken into account.

Many clinicians have theorized that the interval between the start of adjuvant hormone therapy and recurrence is a key factor for determining whether the tumors is exhibiting primary hormone resistance, and the definition of primary hormone resistance was often based on the interval [Bachelot *et al.* 2012; Baselga *et al.* 2012]. However, there has been no clear evidence with regard to the timing and type of resistance. Our results may provide evidence supporting this theory.

Figure 3. The best response to all therapies. (a) The best overall response to all therapies. (b) A comparison of the best response to the therapies between the luminal A subtype and non-luminal A subtypes. (c) A comparison of the clinical benefit rate between the luminal A subtype and non-luminal A subtypes.

Conflict of interest statement

The authors have no conflicts of interest to declare.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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