Original paper

Outcome of Primary Endocrine Therapy in Postmenopausal Patients with Endocrine-responsive Breast Cancer

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Abstract

Purpose: The purpose of this study was to investigate the efficacy and toxicity of primary endocrine therapy in postmenopausal elderly patients with endocrine-responsive breast cancer.

Patients and Methods: The study included 11 postmenopausal patients with breast cancer aged 70 years and over who started primary endocrine therapy between April 2004 and November 2007. Treatment consisted of 1 mg/day anastrozole or 25 mg/day exemestane and was continued until progressive disease was noted. In patients who had progressive disease, another aromatase inhibitor or tamoxifen was administered.

Results: The drugs used as primary therapy were anastrozole and exemestane in 7 and 4 patients, respectively. Seven patients had a performance status of 0 to 1 and 4 had 3 to 4. The best clinical response was a complete remission in 2 patients, in addition to partial remission in 4, stable disease in 4 (including 2 patients with long-term stabilization), and disease progression in 1, with a response rate of 55% and a clinical benefit rate of 73%. The average duration of primary treatment was 15.5 months, and 2 patients died during the study (one from cerebral hemorrhage and the other from breast cancer). With regard to safety, a fracture of the right fourth finger was observed in 1 patient.

Conclusion: Primary endocrine therapy with aromatase inhibitors resulted in a high response rate and a long-term clinical benefit, along with a superior tolerability. Therefore, this therapy can be effective in extremely elderly patients with endocrine-responsive breast cancer.

Key Words: primary endocrine therapy, postmenopausal breast cancer, aromatase inhibitor

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Introduction

The usefulness of endocrine therapy has been established for metastatic breast cancer therapy or as adjuvant therapy for breast cancer^{1,2)}. On the other hand, the concept of primary systemic therapy, in which breast cancer is viewed as a systemic disease and systemic chemotherapy is performed at the early stage of the disease, has recently become increasingly recognized^{3,4)}. However, the risk reduction rate of breast cancer recurrence after chemotherapy is lower in elderly patients, and it may further decrease in patients with endocrine-responsive breast cancer. In addition, since the incidence of endocrine-responsive breast cancer increases with age, the role of chemotherapy for breast cancer in elderly patients may be relatively small. For this reason, a study was conducted by the Group for Research on Endocrine Therapy in the Elderly (GRETA) to compare tamoxifen alone as

a primary endocrine therapy and as postoperative adjuvant therapy in patients with postmenopausal endocrine-responsive breast cancer. The results of this trial showed that primary endocrine therapy with tamoxifen was equally effective, in comparison to therapy administered after surgery⁵⁾. Another clinical trial compared tamoxifen and aromatase inhibitors as primary endocrine therapy, and indicated the superiority of the latter treatment^{6,7)}.

Furthermore, a randomized trial of primary endocrine therapy versus chemotherapy in postmenopausal patients with endocrine-responsive breast cancer demonstrated that both chemotherapy and aromatase inhibitors showed almost equivalent response rates, pathological complete response rates, and breast conservation rates. The adverse events reported were much milder in severity for endocrine therapy⁸⁾.

In Japan, a clinical trial of primary endocrine therapy for breast cancer, national surgical adjuvant study breast cancer 06 (N-SAS BC 06), is in progress: Endocrine therapy is performed preoperatively, and patients who respond well and those with stable disease are randomized into groups with or without chemotherapy to identify

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those who may not need chemotherapy.

In the clinical setting, there are some elderly patients with breast cancer for whom surgery is unfitted or in which the patient refuses surgery. In this department, endocrine therapy is selected as an alternative treatment in such patients. The present study was performed to retrospectively assess the efficacy and toxicity of primary endocrine therapy without preceding surgery in postmenopausal patients with endocrine-responsive breast cancer.

Patients and Methods

The study included 11 patients with breast cancer aged 70 years and over who started primary endocrine therapy because of unfitting for surgery by comorbidity or the refusal of surgery at this department between April 2004 and December 2007. All patients were postmenopausal women with histologically confirmed invasive or noninvasive ductal breast cancer based on a core needle biopsy, with either estrogen receptor (ER) or progesterone receptor (PgR) positive tumors. ER, PgR, and human epidermal growth factor receptor 2 (HER2) were assessed by immunohistochemical staining (IHC). In addition, tumor diameters were measured by ultrasound and calipers. Treatment consisted of 1 mg/day

anastrozole or 25 mg/day exemestane and was continued until disease progression was noted. The clinical effects were evaluated according to the Response Evaluation Criteria in Solid Tumors (RECIST)⁹⁾. However, because many patients did not undergo computed tomography, the tumor size was measured by ultrasonography. A histological examination was performed on the basis of the histopathological criteria for assessment of therapeutic response in breast cancer¹⁰⁾. Adverse events were evaluated according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0¹¹⁾.

Results

The clinicopathological characteristics for all patients are shown in Table 1. The median age of 11 patients was 79 years (range: 72 to 97 years). Six patients (55%) were positive for both ER and PgR, and the remaining 5 (45%) were positive for ER but negative for PgR. IHC for the HER2 status revealed 1+ in 6 (60%), 0 in 2 (20%), and not detected in 2 (20%) out of the 10 patients with invasive carcinoma. HER2 negative was observed in all these patients.

During the study, anastrozole and exemestane were administered in 7 and 4 patients, respectively. Best overall responses were rated as complete response (CR) in 2 patients, partial response (PR) in 4, stable disease (SD) in 4 (including 2 with long-term disease stabilization: SD > or = 24 weeks), and progressive disease in 1, with an overall response rate of 55% and an overall clinical benefit (CR + PR + SD > or = 24 weeks) rate of 73% (Table 2). Surgery was performed in 1 patient, and the histological effect of endocrine therapy was determined to be grade 1b. The average duration of the primary endocrine therapy was 15.5 months, and treatment was discontinued in 5 patients, 1 due to death from another disease and 4 due to exacerbation of the disease.

Two patients died during the study, of which one died from cerebral hemorrhage and the other from an exacerbation of breast cancer. The survival curve in terms of time to progression (TTP) is shown in Figure 1. No exacerbation of the disease was noted in 70% of the patients over more than 24 months. A fracture of the right fourth

Table 1 Clinical and tumor characteristics of 11 patients

	No. of patients	%
Age, years		
Median	79	
Range	72-97	
Tumor status		
Tis	1	9
T1c	2	18
T2	4	36
T3	1	9
T4	3	27
Nodal status		
N0	8	74
N1	1	9
N2a	2	18
Clinical stage		
0	1	9
I	2	18
IIA	4	36
IIIB	3	27
IV	1	9
Hormone receptor status		
ER and PgR both positive	6	55
ER positive PgR negative	5	45
HER2 status (IHC, n=10)		
1+	6	60
0	2	20
unknown	2	20

Table 2 Best Overall response

	Number of patients	%
Complete response	2	18
Partial response	4	36
Stable disease	4	36
(Long SD)	2	18
Progressive disease	1	9
Response rate	55%	
Clinical benefit rate	73%	

SD, stable disease

Fig. 1 Time to progression curve

finger was observed in 1 patient during the study. No morning stiffness or joint pain was reported.

Discussion

Breast cancer treatment is constantly advancing, and primary chemotherapy for this disease is now a standard treatment. Primary endocrine therapy is also attempted in elderly patients with endocrine-responsive breast cancer in which prognostic improvement can hardly be expected with chemotherapy. The problem with pre-operative treatment is that delayed surgery in disease progression cases may adversely affect the prognosis of patients. For this reason, the GRETA trial was conducted to compare tamoxifen alone for primary therapy in postmenopausal elderly patients with endocrine-responsive breast cancer and surgery followed by adjuvant tamoxifen⁵⁾. The trial results showed that at the median follow-up of 80 months the overall survival rates were comparable for these treatment. This trial confirm that because of the significantly high rate of local progression with tamoxifen- alone treatment, minimal surgery followed by adjuvant tamoxifen is the most appropriate treatment in older patients with operable breast cancer. In addition, delayed second-line surgery after primary endocrine therapy does not prejudice the overall survival of the elderly patient.

Aromatase inhibitors have now replaced tamoxifen as the first-line treatment for postmenopausal endocrine-responsive advanced and recurrent breast cancer. Furthermore, preoperative treatment with this class of drugs (letrozole and exemestane) results in a significantly high response rate in comparison to tamoxifen^{6,7)}, and the superiority of aromatase inhibitors was revealed. Because of delayed approval of letrozole in Japan, anastrozole and exemestane were used in the present study with favorable results. Therefore, it is expected that letrozole will probably yield equivalent results.

In recent years, treatments have tended to be performed based on classification of endocrine sensitivity into highly endocrine responsive and incompletely endo-

crine responsive according to the 2007 St. Gallen recommendations²⁾. In the present study, six patients highly responsive to treatment had a response rate of 67% (4pts in 6) and a clinical benefit rate of 83% (5pts in 6), while the remaining five patients who were incompletely responsive to treatment had a response rate of 40% (2pts in 5) and a clinical benefit rate of 60% (3pts in 5), indicating that a high response to treatment is a predictive factor for the clinical efficacy of the endocrine therapy. However, some degree of clinical responses can be expected in incompletely responsive cases, and it may be worth aggressively attempting endocrine therapy with aromatase inhibitor in elderly patients with incompletely endocrine-responsive breast cancer.

Another major advantage of this therapy in addition to the response rates shown above is the longer time to progression. A cure for the targeted disease is not always necessary, and in the present study, the disease state was well controlled for a period of more than 24 months in 70% of the patients.

The adverse events commonly associated with the adjuvant aromatase inhibitor include morning stiffness, joint pain, and hot flush, and were not observed in the present study. This is probably because the study included patients bedridden due to cerebral infarction. Although one patient died from a cerebral hemorrhage, the patient had an advanced age and a past history of hypertension, thus it is impossible to determine if there was a causal relationship between the death and study treatment. It is inevitable that such deaths due to diseases other than breast cancer occurred because of the number of extremely elderly patients included in this study. Another patient who died from breast cancer had chronic heart failure and severe bronchial asthma. Disease progression was noted in this patient after four months of treatment with exemestane. Although the patient was then switched to capecitabine, pleuritis carcinomatosa developed. The patient did not desire further aggressive treatment, and the study treatment was discontinued. The patient died from breast cancer two years and three months after the start of therapy, and the death was considered to be unavoidable in this case.

The number of patients receiving endocrine therapy as preoperative therapy for endocrine-responsive breast cancer should increase in the future. Breast cancer treatment will be proceeded one step beyond the improvement of the survival rate and move towards treatment associated with a higher quality of life.

In conclusion, primary endocrine therapy with aromatase inhibitor for breast cancer performed in the present study resulted in a high response rate and a long-term clinical benefit, along with a superior tolerability. Therefore, this therapy can be aggressively performed in extremely elderly or frail patients who unfit for surgery or refuse surgery.

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