Retrospective Analysis of Concurrent *vs*. Sequential Administration of Radiotherapy and Hormone Therapy Using Aromatase Inhibitor for Hormone Receptor-positive Postmenopausal Breast Cancer

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Abstract. *Background: The optimal sequence of adjuvant aromatase inhibitors and postoperative radiotherapy for postoperative patients with hormone receptor-positive breast cancer treated with breast-conserving surgery is unknown. Patients and Methods: Retrospective analyses of the association of the treatment sequence (concurrent or sequential) of postoperative radiotherapy and adjuvant hormone therapy using aromatase inhibitors with breast cancer outcomes such as ipsilateral breast tumor recurrence, relapse-free and overall survival, and treatment-related complications were performed. Patients were grouped as concurrent (aromatase inhibitors given during radiotherapy followed by continued aromatase inhibitors; 113 patients) and sequential (radiotherapy followed by aromatase inhibitors; 151 patients). Results: At a median follow-up of 2.9 years, there were no differences in the breast cancer outcomes and treatment-related complications between the two treatment groups. In addition, the frequencies of grade 3-5 treatment-related complications were very rare for both treatment groups. Conclusion: Both concurrent and sequential use of postoperative radiotherapy and adjuvant hormone therapy using aromatase inhibitors may be allowed in terms of the breast cancer outcomes and treatment-related complications.*

For breast cancer patients with positive hormone receptor status treated with breast-conserving surgery, adjuvant hormone therapy and postoperative radiotherapy are often used together. However, the optimal sequence of hormone therapy and radiotherapy is unknown. Due to improved disease-free survival, aromatase inhibitors have become standard adjuvant therapy for postmenopausal women with hormone receptor-positive early breast cancer (1, 2). Preclinical results from concurrent treatment with aromatase inhibitors and radiation indicate that this combination therapy could enhance cytotoxicity and improve tumor response (3). However, few clinical data are available on the rationale for the concomitant use of aromatase inhibitors in adjuvant radiotherapy settings.

The aim of this study was to assess the effect of sequencing of aromatase inhibitor therapy and radiotherapy on outcomes in breast cancer and treatment-related complications.

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Patients and Methods

Between October 2001 and August 2008, 1,205 patients with stage I or II unilateral breast cancer underwent breast-conserving surgery at Osaka Medical Center for Cancer and Cardiovascular Disease. Of these patients, 264 postmenopausal patients who underwent breast irradiation and received adjuvant aromatase inhibitor were selected for this retrospective study.

Patients were excluded if the data for the sequencing of their aromatase inhibitor and radiation therapy were unavailable. Only patients with a minimum of 6 months' post-radiotherapy follow-up were included. Patients who also received chemotherapy were included. Any patients with a prior or synchronous contralateral breast cancer or other prior malignancy were also excluded. Patients with noninvasive breast cancer or more advanced disease were not included in this analysis.

Radiotherapy was administered to the breast (not including regional lymph nodes) to a total median dose of 50 Gy in 2-Gy fractions. If the surgical margin resulted in microscopically involved tissue, radiotherapy was followed by an electron beam boost to the primary tumor bed to a total median dose of 63.2 Gy.

Aromatase inhibitors (anastrozole 1 mg or letrozole 2.5 mg) were administered daily for 5 years postoperatively.

Patients were grouped as concurrent (aromatase inhibitors given during radiotherapy followed by continued aromatase inhibitors) and sequential (radiotherapy followed by aromatase inhibitors).

Outcomes for the two groups were compared for any local recurrence, relapse-free survival, and overall survival. Complications were also assessed during treatment and at each follow-up appointment. Grade 3, 4 or 5 pneumonitis, rib fracture, and axillary vein thrombosis were evaluated according to the Radiation Therapy Oncology Group Late Toxicity Criteria (4). Grade 3, 4 or 5 arm edema was assessed according to the National Cancer Institute Common Toxicity Criteria, version 3.0 (5).

Statistical comparisons of clinical, pathological, and treatment-related factors and complications were assessed using the chi square test or Fisher's exact test. Three-year overall survival, relapse-free survival and local failure curves were calculated using the Kaplan-Meier estimates, with time beginning at the surgery. Comparisons for survival curves are based on the log-rank test. All of the statistical tests and *p*-values were two-tailed and *p*-values of <0.05 were considered significant.

Results

Of the 264 patients who were treated with aromatase inhibitors and radiotherapy, 113 were identified as having started aromatase inhibitors before radiotherapy or concurrently with radiotherapy (the concurrent group), whereas 151 received aromatase inhibitors after radiotherapy was completed (the sequential group). Most (97%) of patients were administered anastrozole and 3% of them were administered letrozole. Patients were generally treated with aromatase inhibitors for a total of 5 years, except 8 patients (3%) who were switched to tamoxifen because of adverse events.

Patient characteristics for both the concurrent and sequential study groups of patients are shown in Table I. The concurrent group had a significantly shorter follow-up than the sequential group (2.0 years concurrent *vs*. 3.4 years sequential; $p<0.0001$). Moreover, the concurrent group also had significantly more progesterone receptor-positive tumors (74% concurrent *vs*. 60% sequential; $p<0.04$). Between the two treatment groups, there were no different frequencies of chemotherapy use (17% both), but types of chemotherapy regimens were different. A taxane-based regimen was used more frequently in the concurrent group (37% concurrent *vs*. 0% sequential). Other clinicopathological factors were similar in the two groups (all $p>0.1$).

At a median follow-up of 2.9 years, out of the 113 patients in the concurrent group, there was no death; while in the 151 patients in the sequential group, there was 1 death. Relapse in the ipsilateral breast was observed in 1 patient of the concurrent group, whereas no patient in the sequential group experienced local relapse. One patient in the concurrent group developed regional relapse, whereas 2 patients in the sequential group developed regional relapse. Distant metastasis was observed in 1 patient in the concurrent group compared with 3 patients in the sequential group. The sequence of therapy did not influence the 3-year ipsilateral breast tumor recurrence rate (both 0%; *p*-value could not be calculated), overall survival (both 100%; *p*-value could not be calculated), or relapse-free survival (concurrent, 100%; sequential, 98%; $p=0.68$).

Toxicities were reviewed by the sequence of aromatase inhibitor and radiotherapy. No significant differences were observed in grade 3 to 5 toxicity between the two cohorts,

Table I. *Patient and tumor characteristics of patients receiving aromatase inhibitors and radiotherapy.*

	Concurrent n (%)	Sequential n (%)	*p*-Value
No. of patients	113	151	
Age, years			
Median	60	60.5	0.87
Range	48-81	49-80	
Median follow-up, years	2.0	3.4	<0.0001
T-stage			
T1	67 (59)	82 (54)	0.68
T2	43 (38)	62 (41)	
T3	2 (2)	3 (2)	
Unknown	1 (1)	4 (3)	
Positive node status			
0	83 (73)	113 (75)	0.91
1-3	18 (16)	26 (17)	
4+	6 (5)	5 (3)	
Unknown	6 (5)	7 (5)	
Pathology			
Infiltrative ductal	108 (96)	142 (94)	0.84
Other	2 (2)	4 (3)	
Unknown	3 (3)	5 (3)	
Surgical margins			
Negative	106 (94)	135 (89)	0.37
Positive	7 (6)	15 (10)	
Unknown	0 (0)	1 (1)	
Estrogen receptor status			
Negative	2 (2)	8 (5)	0.31
Positive	110 (97)	141 (93)	
Unknown	1 (1)	2 (1)	
Progesterone receptor status			
Negative	28 (25)	59 (39)	0.04
Positive	84 (74)	90 (60)	
Unknown	1 (1)	2 (1)	
Total radiation dose (Gy)			
50	107 (95)	141 (93)	0.66
63.2	6 (5)	10 (7)	
Adjuvant chemotherapy			
No	94 (83)	125 (83)	0.93
Yes	19 (17)	26 (17)	
Type of chemotherapy			
CMF	0 (0)	1(4)	0.008
Taxane-based	7 (37)	0 (0)	
Anthracycline-based	10 (53)	21 (81)	
Combination of anthracycline and taxane	2 (11)	4 (15)	

CMF: Cyclophosphamide, methotrexate, 5-fluorouracil.

with 2 out of 113 (2%) in the concurrent group compared with 1 out of 153 (1%) in the sequential group (p=0.40). Grade 3 to 5 rib fracture, and axillary vein thrombosis did not occur in either group. Grade 3 pneumonitis occurred in 1 patient (1%) of the concurrent group and none of the sequential group. Grade 3 arm edema occurred in 1 patient of each group.

Discussion

Hormone therapy and radiotherapy are both quite important for breast cancer patients treated with breast-conserving surgery and whose tumors are hormone receptor positive. However, to date, the optimal sequence of hormone therapy and radiotherapy is unknown.

Over three decades, tamoxifen has been used for the treatment of early breast tumors that are positive for hormone receptor in premenopausal and postmenopausal women, and the effect of tamoxifen on overall survival has been established in the adjuvant therapy of breast cancer (6).

However, there are little data regarding the effect of timing of tamoxifen and radiotherapy. Although some basic studies have demonstrated reduced radiosensitivity of human tumor cells pretreated with tamoxifen, others have suggested enhanced radiosensitivity (7-9). To date, no randomized trials have investigated the clinical effect of the sequencing of tamoxifen and radiotherapy. Retrospective studies suggest that in practical application, concurrent administration of tamoxifen with radiotherapy does not compromise breast cancer outcomes (10-12) but might increase subclinical toxicity (13, 14).

This question of sequencing of hormonal therapy and radiation is still a clinical concern because of the increasing use of aromatase inhibitors. Several recent randomized controlled trials showed that aromatase inhibitors were superior to tamoxifen in terms of improved disease-free survival for postmenopausal patients with hormone receptor-positive tumors (1, 2). To date, there are few clinical data regarding the effect of the sequencing of aromatase inhibitors and radiotherapy (15). To our knowledge, this is the first such report. No significant differences were observed in ipsilateral breast tumor recurrence rates, overall survival and relapse-free survival between the two cohorts. In addition, the incidence of clinically relevant complications from the use of aromatase inhibitors and radiotherapy was very low in both the treatment groups. Results of this retrospective analysis are similar with findings from the reports of tamoxifen and radiotherapy (10-12).

This study has several limitations. The major limitations are a small sample size and short follow-up period. In addition, the important limitation of this study is the difference of the length of follow-up between the two cohorts. Patients treated with radiation therapy and aromatase inhibitors sequentially were observed for a significantly longer period of time (3.4 *vs*. 2.0 years; p<0.0001). Due to this difference, chemotherapy regimens were different. In the concurrent group, more patients were administered newer chemotherapy regimens (taxane-based), and fewer patients were treated with anthracycline-based regimens (16). If taxane-based regimens were superior to anthracycline-based regimen in terms of breast cancer outcomes, the concurrent group could have a better outcome. Due to a gradual shift in practice pattern over time, the frequency of the concurrent use of aromatase inhibitors and radiotherapy was increasing after several reports regarding the sequencing of tamoxifen and radiotherapy have been published (10-12).

Despite several limitations, this retrospective analysis may suggest that between the two treatment modes (concurrent or sequential use), there were no differences in the breast cancer outcomes and treatment-related complications.

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