Original Article

Effect of Chemotherapy for Luminal A Breast Cancer

Naotaka Uchida,*† Takako Suda† and Kiyosuke Ishiguro†

*Clinic of Surgery, Tottori Prefectural Kosei Hospital, Kurayoshi 682-0804, Japan and †Clinical Department of Mammoendocrinology, Tottori University Hospital, Yonago 683-8504, Japan

ABSTRACT

Background   The addition of chemotherapy to endocrine therapy for luminal A breast cancer generally provides little benefit. However, the least benefit of chemotherapy in all patients with luminal A breast cancer is controversial.

Methods   This was a retrospective study of 140 patients with luminal A breast cancer who underwent surgery at Tottori University Hospital between 2001 and 2010. Luminal A breast cancer was defined as positive for estrogen receptors and/or progesterone receptors and negative for human epidermal growth factor 2. Postoperative endocrine therapy was given to all patients. The prognostic values of age, tumor size, presence of lymphovascular invasion and lymph node status were evaluated. In addition, the prognostic value of chemotherapy for patients with identified risk factors affecting relapse-free survival and overall survival was evaluated.

Results   Tumor size greater than 2 cm and positive lymph node status were factors significantly affecting relapse-free survival. There were no factors significantly affecting overall survival. There was no significant difference in the relapse-free survival of patients with tumor size greater than 2 cm and/or positive lymph node status who either received chemotherapy or not. However, the relapse event was earlier in patients with tumor size greater than 2 cm and positive lymph node status who did not receive chemotherapy than in those who received chemotherapy.

Conclusion   Chemotherapy could provide little benefit to patients with luminal A breast cancer. However, chemotherapy may bring them longer relapse-free periods.

Key words   breast cancer; chemotherapy; luminal A

Luminal A breast cancers that express estrogen receptors (ERs) and/or progesterone receptors (PRs) and are negative for human epidermal growth factor receptor 2 (HER2) expressions respond well to endocrine therapy and have a generally favorable prognosis. Patients with luminal A breast cancers are not so sensitive to paclitaxel- and doxorubicin-containing preoperative chemotherapy.[1] Patients with node-positive luminal A breast cancer gain little benefit from taxane therapy administered.[2, 3] Proceedings from the 12th St. Gallen International Breast Cancer Conference held in 2011 showed that the luminal A subtype was fairly unresponsive to chemotherapy and said that node positivity per se was not an indication for use of chemotherapy, although a large majority of physicians would use it if more than 3 axillary lymph nodes were involved.[4] However, the least benefit of chemotherapy in all patients with luminal A breast cancer is controversial. The 11th St. Gallen Conference held in 2009 presented the relative indications for using endocrine therapy alone or a combination of chemotherapy and endocrine therapy for luminal A breast cancer.[5] The clinicopathological risk factors for prognosis included lymph node status, tumor size, presence of lymphovascular invasion, histological grade, and proliferative status. Therefore, it is essential to clarify the significance of chemotherapy for patients with these risk factors and luminal A breast cancer. In this report, we analyzed the significance of chemotherapy for patients with luminal A breast cancer who underwent surgery and received postoperative endocrine therapy.

SUBJECTS AND METHODS
Patients
A total of 140 patients with initial luminal A primary invasive breast cancers who underwent surgery in our department at Tottori University Hospital between June 2001 and December 2010 were retrospectively investigated (Table 1). Men with breast cancer, women with in situ carcinoma, bilateral breast carcinoma or who underwent neoadjuvant chemotherapy or chemotherapy for another disease were excluded from the study. Informed consent was obtained from every patient. Patients were treated with breast-conserving surgery or mastectomy. All patients received post-operative endocrine therapy (Table 2). Most patients with breast-conserving surgery received radiotherapy to the whole breast after surgery. There were 24 patients who received chemotherapy (Table 2). Decisions regarding chemotherapy were made by the treating physician on the basis of patient preference

Table 1. Patients characteristics

		Median [range]		Number	(%)
Age (yr)		60.5	[34–86]		
Menstruation status	Premenopause			39	(28%)
	Postmenopause			101	(72%)
Surgical procedure	Mastectomy			39	(28%)
	Breast-conserving surgery			101	(72%)
Tumor size (cm)		1.7	[0.5–5.3]		
ER positivity proportion (%)		90	[15–95]		
PR positivity proportion (%)		60	[0–95]		
Lymphovascular invasion	Negative			37	(27%)
	Positive			101	(72%)
	Unkown			2	(1%)
Nuclear grade	Grade 1			52	(37%)
	Grade 2			54	(39%)
	Unkown			34	(24%)
Ki67	< 14%			18	(13%)
	Unknown			122	(87%)
Lymph node metastasis status	Negative			103	(74%)
	Positive			37	(26%)
Lymph node metastasis number*		2	[1–18]		

* Number in 37 positive cases.
ER, estrogen receptor; PR, progesterone receptor.

or nuclear grade were determined, the luminal A subtype was also defined as low Ki-67 labeling index (< 14%) and/or nuclear grade 1 or 2. ER and PR positivity was confirmed by immunohistochemistry (IHC); greater than 10% of tumors cells staining positive was considered positive. HER2-negative-status was confirmed by IHC (with 0, 1+, 2+ scores indicating no cells with staining, < 10% of cells with membrane staining, or > 10% of cells with low or medium membrane staining, respectively). Tumors that were 2+ by IHC were also examined by fluorescence in situ hybridization (with an amplification ratio < 2.0 indicating negative status). The Ki-67 labeling index was determined by IHC.

and risk factors. In principle, the chemotherapy regimen was as follows: FEC (fluorouracil 500 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2) alone on day 1 every 3 weeks for 4 cycles or FEC (fluorouracil 500 mg/m^2, epirubicin 60 mg/m^2 and cyclophosphamide 500 mg/m^2) on day 1 every 3 weeks for 4 cycles followed by docetaxel (60 mg/m^2) on day 1 every 3 weeks for 4 cycles or paclitaxel (80 mg/m^2) on day 1 and 8 every 3 weeks for 4 cycles.

Histopathological and immunohistochemical evaluations

All histopathological and immunohistopathological diagnoses were determined by several pathologists at our facilities or at another laboratory facility within our partnership. Surgical specimens were embedded in paraffin, sectioned and stained with hematoxylin and eosin. Luminal A subtype was defined as ER and/or PR positive and HER2 negative. If the Ki-67 labeling index and/

Statistics

Relapse-free survival was defined as the period from the date of operation to the date of the first confirmation of relapse (i.e., local relapse or metastasis) or death from any cause, whichever came first. Overall survival was defined as the period from the date of operation to the date of death from any cause. Relapse-free and overall survival periods were estimated with the Kaplan-Meier method and compared with the log-rank test and Wilcoxon test. The Mann-Whitney U test was used for comparisons of continuous outcomes, while the chi-square test, for comparisons of categorical variables. Risk factors affecting prognosis were estimated with univariate and multivariate analyses. Cox's proportional-hazards model was applied in multivarate analysis. Differences were considered significant when the P value was < 0.05.

Table 2. Adjuvant systemic therapy

		Number	(%)
Endocrine therapy [n = 140]	Tamoxifen ± LH-RH agonist	48	(34%)
	Aromatase inhibitor	75	(54%)
	Tamoxifen ± LH-RH agonist → Aromatase inhibitor	15	(10%)
	Aromatase inhibitor → Tamoxifen	1	(1%)
	Toremifene citrate	1	(1%)
Chemotherapy [n = 24]	Anthracyclin	19	(79%)
	Anthracyclin + Taxane	5	(21%)

LH-RH, luteinizing hormone-releasing hormone.

Table 3. Comparion between chemotherapy and non-chemotherapy groups

Factor		Chemotherapy group n = 24		Non-chemotherapy group n = 116		P value
Number of lymph node metastasis	Median [range]	1.5	[0–18]	0	[0–8]	< 0.01
Tumor size (cm)	Median [range]	2.5	[1.2–4.5]	1.5	[0.5–5.3]	< 0.01
Lymphovascular invasion	Positive: number (%)	23	(96%)	78	(67%)	< 0.01
	Negative: number (%)	1	(4%)	36	(31%)	
	Unknown: number (%)			2	(2%)	
Age (yr)	Median [range]	52	[34–74]	62	[37–86]	< 0.01
Event	Relapse: number (%)	4	(16%)	6	(5%)	0.06
	Death: number (%)	2	(8%)	3	(2.5%)	0.2

RESULTS

Patient characteristics

Table 1 shows the characteristics of 140 luminal A breast cancer patients. The median patient age was 60.5 years (range: 34–86 years). Menstruation status of 39 (28%) patients was premenopausal and that of 101 (72%) patients was postmenopausal. There were 101 (72%) patients receiving breast-conserving surgery and 39 (28%) patients receiving mastectomy. The median tumor size was 1.7 cm (range: 0.5–5.3 cm), and 103 patients (74%) were free of axillary lymph node metastasis. In 37 patients with axillary lymph node metastasis, the median number of involved lymph nodes was 2 (range: 1–18). Median ER and PR positivity proportions of tumor cells in each tumor were 90% (range: 15–95%) and 60% (range: 0–95%) respectively. There were 101 (72%) patients positive for lymphovascular invasion. There were 52 (37%) and 54 (39%) patients with nuclear-grade tumors of 1 and 2, respectively. The median follow-up period was 40 months (range: 3–113 months).

Adjuvant systemic therapy

Table 2 lists the post-operative systemic therapies. All patients received some type of endocrine therapy. A total of 48 (34%) patients received tamoxifen and/or a luteinizing hormone-releasing hormone agonist, and 75 (54%) patients received an aromatase inhibitor. There were 15 (10%) patients who changed from tamoxifen and/or luteinizing hormone-releasing hormone agonist to the aromatase inhibitor for the following reasons: change from

pre- to post-menopausal in 9 patients, patient preference to continue endocrine therapy after 5 years of treatment with 1 type of therapy in 3, thrombosis in 1, uterine endometrial hypertrophy in 1, and uterine cancer in 1 patients. One patient changed from the aromatase inhibitor to tamoxifen because of joint pain.

A total of 24 patients received chemotherapy. Chemotherapy was performed more frequently to patients with metastases involving several lymph nodes, large tumor size, positive lymphvascular invasion and younger age (Table 3). Relapse events were 4 (16%) in the chemotherapy group and 6 (5%) in the non-chemotherapy group, and intergroup difference was not significant (P = 0.06) (Table 3). Death events, 2 (8%) in the chemotherapy group and 3 (2.5%) in the non-chemotherapy group, showed no significance (P = 0.20) (Table 3). Of 24 chemotherapy-based patients, 19 (79%) patients received anthracycline alone, and the remaining 5 (21%) received anthracycline and taxane (Table 2). Chemotherapy that included taxane was adopted more frequently in patients with metastases involving several lymph nodes: median number of involved nodes (range) was 1 (0–13) when the agent was anthracycline, and 11 (3–18) when taxane was coadministered.

Risk factors associated with relapse and death

Relapse or death risk factors were investigated by univariate analysis among positive lymph node status, tumor size > 2 cm, positive lymphovascular invasion and age < 40 years old. As the result, positive lymph node status and tumor size > 2 cm were significant relapse

Table 4. Relapse-free survival and overall survival in 140 patients with luminal A breast cancer (univariate analysis)

	Relapse-free survival			Overall survival		
	Univariate analysis			Univariate analysis		
	Hazard ratio	95% Confidence interval	P value	Hazard ratio	95% Confidence interval	P value
Lymph node status (positive versus negative)	8.08	2.02–32.2	< 0.01	4.68	0.66–32.7	0.11
Tumor size (> 2 cm versus ≤ 2 cm)	3.68	1.01–13.3	0.04	1.73	0.26–11.3	0.56
Lymphovascular invasion (positive versus negative)	1.98	0.43–9.04	0.37	1.57	0.21–11.5	0.65
Age (< 40 yr versus ≥ 40 yr)	0.35	0.01–8.04	0.51	0.35	0.001–122.9	0.72

Table 5. Relapse-free survival and overall survival in 140 patients with luminal A breast cancer (multivariate analysis)

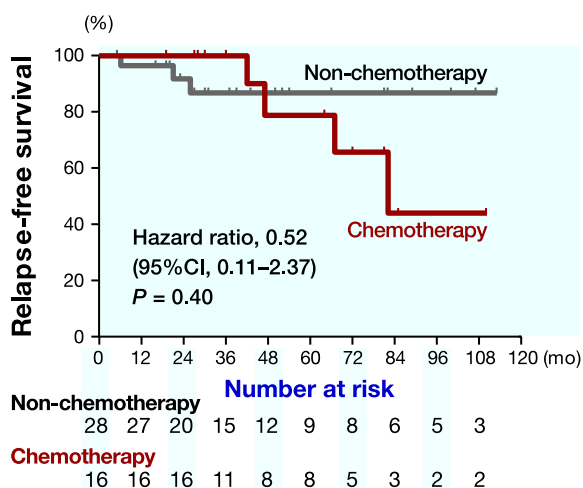|	Relapse-free survival			Overall survival		
	Multivariate analysis			Multivariate analysis		
	Hazard ratio	95% Confidence interval	*P* value	Hazard ratio	95% Confidence interval	*P* value
Lymph node status (/1 involved node)	0.95	0.88–1.03	0.26	0.94	0.88–1.01	0.14
Tumor size (/1 cm)	0.88	0.68–1.15	0.37	0.89	0.69–1.15	0.39
Lymphovascular invasion (positive versus negative)	0.84	0.56–1.26	0.40	0.86	0.57–1.30	0.49
Age (/1 yr)	1.01	0.99–1.02	0.14	1.01	0.99–1.02	0.12

Fig. 1. Relapse-free survival in patients with tumor sizes > 2 cm. There is no difference between groups undergoing chemotherapy or not.
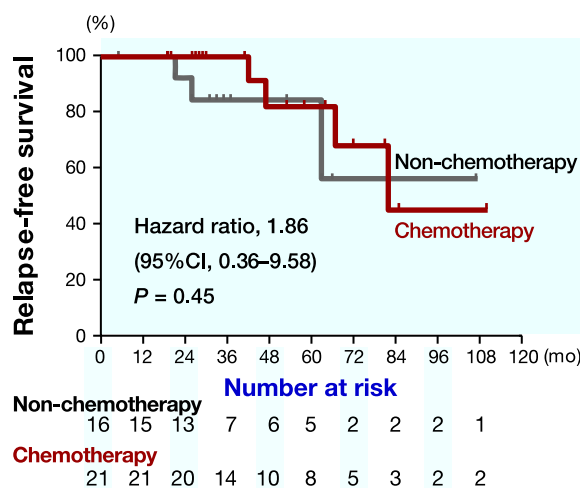

Fig. 2. Relapse-free survival in patients with axillary lymph node metastasis. There is no difference between groups undergoing chemotherapy or not.

risk factors (Table 4). Meanwhile, there were no significant death risk factors (Table 4). In multivariate analysis, there were no significant relapse and death risk factors (Table 5).

Relapse-free survival

The relapse-free survival rates of patients with significant risk factors were estimated for patients with or without chemotherapy. In 44 patients with tumor size > 2 cm, 16 patients received chemotherapy. The 5-year relapse-free survival rate of the patients undergoing chemotherapy was estimated at 78.7%, whereas for those not undergoing chemotherapy it was estimated at 86.6%. The difference was not significant (*P* = 0.40) (Fig. 1).

In 37 patients with positive lymph node status, 21 patients received chemotherapy. The 5-year relapse-free survival rate of the patients undergoing chemotherapy was estimated at 82.5%, whereas for those not undergoing chemotherapy it was estimated at 83.3%. The difference was also not significant (*P* = 0.45) (Fig. 2).

In 20 patients with positive lymph node status and tumor size > 2 cm, 14 patients received chemotherapy. The 5-year relapse-free survival rate of the patients undergoing chemotherapy was estimated at 78.7%, whereas
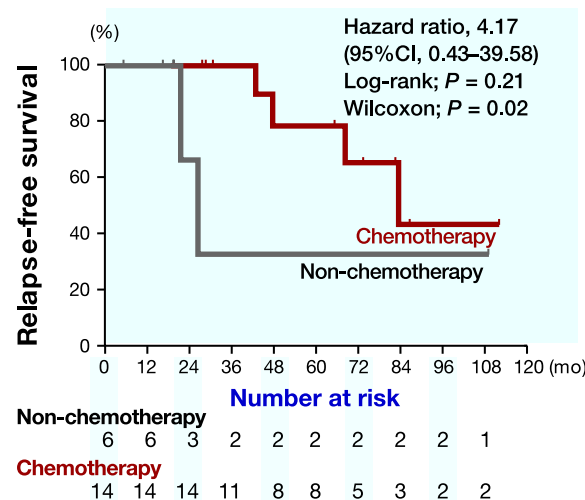

Fig. 3. Relapse-free survival in patients with tumor sizes > 2 cm and axillary lymph node metastasis. There is no difference between groups undergoing chemotherapy or not. But chemotherapy brings a longer relapse-free period.

for those not undergoing chemotherapy it was estimated at 33.3%. The difference was also not significant on log-rank analysis (*P* = 0.21), but significant on Wilcoxon's analysis (*P* = 0.02) (Fig. 3). These suggest earlier relapse

were more frequent in non-chemotherapy group than chemotherapy group.

DISCUSSION

Using complementary DNA microarrays representing 8102 human genes, Perou et al. defined 4 breast cancer subtypes (luminal/ER, HER2-overexpressing, basal-like and normal), based on gene expression patterns.[6] Carley et al. subsequently classified 5 subtypes based on immunohistochemical staining of various markers as follows: luminal A (ER+ and/or PR+, HER2–), luminal B (ER+ and/or PR+, HER2+), HER2 (ER–, PR–, HER2+), basal-like (ER–, PR–, HER2–, CK5/6+ and/or HER1+) and an unclassified type, and also demonstrated the applicability of this system to past classification systems based on gene microarray analysis.[7] The clinical application of gene expression profiling is limited because the procedure is technically difficult and expensive. Therefore, the consensus of the 12th St. Gallen Conference defined luminal A breast cancer as ER+ and/or PR+, HER2– tumors with a Ki-67 labeling index of < 14%.[4] However, there was a lack of complete consensus on the threshold indication for administering chemotherapy to patients with luminal A breast cancer.[4] It has been reported that Oncotype DX recurrence scores were high in 13% of patients with luminal A breast cancer.[8] Among tamoxifen-treated patients, patients with a low or intermediate recurrence score on the 21-gene assay benefited from tamoxifen, whereas patients with a high recurrence score did not benefit.[9] However, the 21-gene assay has also demonstrated that chemotherapy provided a large benefit when the recurrence score was high.[10] These results suggest that chemotherapy is beneficial for patients with potentially malignant luminal A breast cancer.

The value of chemotherapy for patients with large luminal A breast tumors is unclear. The 21-gene recurrence score assay has shown that there is a significant association between increased tumor size and high recurrence score.[10] Tumor size was prognostic for local and distant relapse.[11, 12] These findings suggest that the larger the tumor the greater the association of gene expression with malignant potential and that chemotherapy may lead to a better prognosis. However, in our study, chemotherapy had no beneficial effects on relapse in patients with tumors larger than 2 cm.

The value of chemotherapy for patients with lymph node involvement of luminal A breast cancer is also not clear. Generally speaking, the number of axillary lymph node metastases is the most reliable prognostic factor and an important indication for adjuvant therapy. The addition of a paclitaxel protocol after the completion of anthracycline treatment has improved the disease-free and OS of patients with node-positive early breast cancer.[13, 14] However, patients with luminal A breast cancer benefit less from treatment with a taxane when administered after anthracycline, even if lymph nodes are involved.[2, 3] In our study, chemotherapy had no beneficial effects on relapse in patients with lymph node involvement. The effects on relapse in patients with large tumor size and lymph node involvement were also not beneficial. Multivariate analysis revealed that endocrine therapy alone sufficiently removed relapse and death risk from patients with luminal A breast cancer.

The following reasons could explain why, in our study, patients with larger tumors and lymph node involvement did not benefit from chemotherapy. First, microarray analysis has shown that nodal status and tumor size cannot be correlated with biologically distinct diseases.[15] These findings suggest that biological characteristics, not node positivity, are indications for the use of chemotherapy.[4] Therefore, in our study, luminal A breast cancer in patients with larger tumors and lymph node involvement may exhibit lower malignant potential. Second, the chemotherapy regimen used in this study was at the lower limit of standard regimens in regard to dosages (epirubicin: 60–100 mg/m^2, docetaxel: 60–100 mg/m^2, paclitaxel: 80–100 mg/m^2). A less-efficacious regimen might be the reason that we did not detect a significant effect in the chemotherapy group. Third, the size of this study is a limitation. Our study is retrospective, and the chemotherapy group contained 24 patients. We cannot draw a conclusion using such a small dataset. Fourth, unknown cases regarding nuclear grade and/or Ki-67 could affect the results. In our study, nuclear grade in 34 patients was unknown because the grading is generally used in patients with invasive ductal carcinoma and there is no consensus to decide nuclear grade in patients with special types of breast cancer. Ki-67 in 122 patients was unknown because it was introduced in May 2009, and the confidence for specimens embedded in paraffin and preserved for long time is not established. Ki-67 and/or nuclear grade are important factors to distinguish luminal A and luminal B (HER2 negative type) in the 12th St. Gallen International Breast Cancer Conference held in 2011. Among them, the cases belonging to luminal B (HER2 negative type) could be included and it may influence the result in patients with large tumor size and lymph node involvement.

In conclusion, chemotherapy could provide little benefit to patients with luminal A breast cancer, even those with high relapse risk factors including large tumor size and many positive nodes. However, chemotherapy may bring patients longer relapse-free periods. Prospec-

tive studies and additional subject recruitment are necessary to draw definitive conclusions.

The authors declare no conflict of interest.

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