JBUON 2018; 23(4): 877-882
ISSN: 1107-0625, online ISSN: 2241-6293 • www.jbuon.com
E-mail: editorial_office@jbuon.com

ORIGINAL ARTICLE

Is adjuvant chemotherapy necessary for Luminal A-like breast cancer?

Halil Taskaynatan[1], Yuksel Kucukzeybek[1], Ahmet Alacacioglu[1], Yasar Yildiz[1], Tarik Salman[1], Utku Oflazoglu[1], Umut Varol[1], Betul Bolat Kucukzeybek[2], Murat Kemal Atahan[3], Mustafa Oktay Tarhan[4]

[1]Department of Medical Oncology, [2]Department of Pathology, [3]Department of General Surgery, Izmir Katip Celebi University, Ataturk Training and Research Hospital, Izmir, Turkey; [4]Institute of Oncology, Dokuz Eylul University, Izmir, Turkey

Summary

Purpose: *Patients with breast cancer with Luminal-A subtype have a better prognosis but poor chemotherapy response. Chemotherapy is controversial in lymph node-positive patients with Luminal-A subtype. In this retrospective study, we aimed to evaluate the efficacy and benefit of chemotherapy in the Luminal A-like subtype of breast cancer.*

Methods: *Patients diagnosed with breast cancer within 2006 and 2011 were retrospectively evaluated. Patients with pathologically confirmed Luminal A-like breast cancer were analyzed , and were divided in those receiving taxane-based adjuvant chemotherapy and those who did not.*

Results: *A total of 136 patients with Luminal-A type were included in the study. The 10-year cumulative disease-free survival (DFS) was 85.6 vs 96.7% (p=0.230) for the chemotherapy and non-chemotherapy groups, and overall survival (OS) was 88.6 vs 100%, respectively (p=0.242). The 10-year cumulative DFS was 80 vs 98.1% for the taxane-based chemotherapy group and taxane-free chemotherapy group (p=0.501), while the OS was 87.5 vs 95.2%, respectively (p=0.391). There was a positive correlation between relapse status and lymph node involvement in the multivariate analysis (p=0.031).*

Conclusion: *Adjuvant chemotherapy in Luminal-A showed no significant difference for DFS and OS. Taxane-based chemotherapy did not demonstrate any benefit for OS and DFS with relatively more advanced stage and lymph node involvement. We believe that adjuvant chemotherapy plays a minor role in a significant proportion of Luminal-A subtype of breast cancer.*

Key words: *adjuvant chemotherapy, breast cancer, Luminal A-like*

Introduction

Breast cancer is the second most common cancer in the world, and 1.67 million new cases of breast cancer were reported in 2012 [1]. Adjuvant chemotherapy reduces recurrence rates in patients with breast cancer [2]. Since 1990, it has been proven that anthracycline-containing chemotherapy is superior to standard cyclophosphamide, methotrexate and fluorouracil [CMF] [3]. The addition of a taxane (paclitaxel or docetaxel) comes up with further improvement of patient outcomes in the adjuvant treatment [4,5]. Nevertheless, some patients do not benefit from this adjuvant treatment and a need has arisen to determine predictive biomarkers [6].

Since chemotherapy started to be included in the adjuvant therapy for breast cancer [7], it has been considered useful in only a portion of patients receiving chemotherapy depending on

Correspondence to: Yuksel Kucukzeybek, MD. Izmir Katip Celebi University, Ataturk Training and Research Hospital, Medical Oncology Clinic, 35360 Izmir, Turkey.
Tel:+ 90 232 243 43 43, E-mail:drzeybek@yahoo.com
Received: 27/09/2017; Accepted: 25/11/2017

the risk of recurrence. A significant amount of research has been conducted over the past decade using gene expression assays or extended immunohistochemical tests to better identify patients who will receive chemotherapy [8].

As part of tumor heterogeneity, multiple microarray gene expression profiling studies have also shown that different molecular subtypes of breast cancer are associated with different prognoses and the possibility of responding to systemic treatment [9]. Classifying the subgroups of breast cancer according to the gene expression pattern is the gold standard, but both the research and the clinical use of the gene expression profile remain limited. The gene expression profile is not widely used as it is technically difficult and costly. For this reason, the use of immunohistochemical markers is of greater interest to classify the tumor into subtypes [10].

At the 2013 St Gallen International Breast Cancer Conference, Luminal A-like subtype was defined with the following parameters: Estrogen receptor (ER) >1%, progesterone receptor (PR) ≥20%, human epidermal growth factor receptor-2 (HER2) negative and Ki-67 <14% [11]. On the other hand, in the 2015 St Gallen consensus, the Luminal A-like high ER / PR is expressed as low Ki67 index. While the panel did not recommend a cut-off value for PR, Ki-67 scores should be interpreted according to local laboratory values [12].

Compared with other subtypes, patients with Luminal-A subtype present a better prognosis but the response to chemotherapy is low [13]. Patients with lymph node positivity in ER-positive breast cancer respond better to chemotherapy than the negative patients [14]. However, the role of adjuvant chemotherapy in lymph-node-positive Luminal-A subtype breast cancer is controversial [13]. In this retrospective study we aimed to evaluate the efficacy and benefit of chemotherapy in breast cancer Luminal A-like subtype.

Methods

Patient population

We retrospectively evaluated the patients with breast cancer who were admitted to the medical oncology outpatient clinic of Izmir Ataturk Training and Research Hospital between 2006 and 2011. Patients with pathologically confirmed ER and PR positivity and HER2-negative invasive breast cancer were analyzed. The study was approved by the local Institutional Review Board.

Molecular subtypes of breast cancer were categorized according to ER, PR, and HER2 status. Patients with ER, PR positive and HER 2 negative and Ki67 level <14% were defined to have Luminal A-like disease and were included in the study [11]. Patients were excluded if they had *in situ* breast cancer (e.g., ductal carcinoma *in situ*), neoadjuvant chemotherapy, radiation therapy prior to surgery, lost to follow-up, metastatic disease or a molecular subtype other than Luminal-A. Additionally, those patients with incomplete immunohistochemistry (IHC) or fluorescence *in situ* hybridization (FISH) data for evaluating HER2 and hormone receptor status were also excluded. If the Ki-67 level could not be assessed by a pathologist, histologically grade 1 patients were defined as Luminal A-like breast cancer.

Immunohistochemistry analysis

The IHC staining was performed using standard streptavidin–biotin-peroxidase method on 3–5-mm thick tissue sections. The staining sources and dilutions for the antibodies used are as follows: ER (Clone SP1, 1:40, Novocastra, Newcastle upon Tyne, UK), PR (Clone SP2, 1:100, Novocastra), HER2 (Clone CB11, 1:40, Novocastra), and Ki-67 (Clone MIB1, 1:200, Novocastra). ER and PR statuses were recorded according to the pathologist's interpretation of the assays. ER and PR were considered negative if the staining of tumor cell nuclei was less than 1%. A negative HER-2 expression was identified with no membranous staining (negative) or those that either had some staining in <10% of tumor cells or had weak-to-moderate staining (1+). Those who had moderate staining in >10% of cells (2+) were further evaluated by FISH for gene amplification. FISH was scored on a quantitative scale with less than two copies of the HER-2 gene classified as negative. The Ki-67 proliferation index was assessed using a 40x objective lens with the highest area of staining (hot spot).

Statistics

Statistical analyses were performed using the SPSS 21 software. Student's t-test was used to compare parametric data matching normal distribution and Mann-Whitney U test was used to evaluate non-normal distribution data in independent samples. The DFS and OS rates for the entire population and patient subgroups were calculated by the Kaplan-Meier method and compared with log-rank test. Univariate and multivariate Cox regression analyses were performed to identify the independent prognostic factors for DFS and OS. All statistical tests were two-sided, and a p-value <0.05 was considered as statistically significant.

Results

A total of 136 patients with Luminal-A type were included in the study. All patients received hormonal therapy with or without chemotherapy. Of these, 104 (76.5%) underwent adjuvant chemotherapy, and 32 (23.5%) did not. The median age of patients was 50 years (range: 27-75) for the adjuvant chemotherapy receiving group and 49 (range: 35-75) for the non-chemotherapy group. Approximately half of the patients in both patient groups who received or did not receive chemotherapy

were postmenopausal. Lymph node involvement (p=0.001), pathologic T stage (p<0.001) and disease stage (p<0.001) were more advanced in the group that received chemotherapy. All baseline patient characteristics are shown in Table 1.

There was no significant difference between DFS and OS between the two groups. The 10-year cumulative DFS was 85.6 vs 96.7 % (p=0.230, Figure 1A) and OS was 88.6 vs 100% (p=0.242, Figure 1B) for the groups with and without chemotherapy, respectively. While one relapse occurred in the non-chemotherapy group, 10 patients relapsed and 4 died in the group that received chemotherapy. No death was reported among the patients who did not receive chemotherapy during the study.

A total of 104 patients received adjuvant chemotherapy. Of these, 43 (41%) received taxane-based chemotherapy and 61 (59%) taxane-free chemotherapy. While there was no difference in menopausal status, age, histologic grade and pathologic T stage in the taxane-based chemotherapy arm and taxane-free chemotherapy arm, disease stage (p <0.001) and lymph node involvement (p <0.001) were more advanced in the former. Clinical characteristics of patients receiving chemotherapy are shown in Table 2.

There was no significant difference between DFS and OS between the two groups. The 10-year cumulative DFS was 80 vs 98.1% for the groups that received taxane-based chemotherapy and taxane-free chemotherapy (p=0.501, Figure 2A); OS was 87.5 vs 95.2% for the two groups (p=0.391, Figure 2B). In the group receiving taxane-based chemotherapy, 6 patients developed recurrence and one patient died. In the taxane-free chemotherapy group, 5 patients developed recurrence and 3 died. There was a positive correlation between relapse status and lymph node involvement in the multivariate analysis (p=0.031).

Discussion

The present study revealed no significant difference between DFS (p=0.230) and OS (p=0.242) for Luminal-A subtype in those breast cancer patients who had systemic treatment in addition to hormonotherapy. Similarly, there was no difference in terms of DFS (p=0.501) and OS (p=0.391) in patients treated with and without a taxane-based combination. In the present study, all the cases were Luminal-A-like patients. Although patients with the Luminal-A subtype have a better prognosis, their response to chemotherapy remains low [13].

Although lymph node metastasis is seen in Luminal-A subtype breast cancer, the choice of adjuvant chemotherapy or endocrine therapy alone still needs clarification. There is limited information on the effects of adjuvant chemotherapy to patient outcomes [15]. In our study, there was no advantage in terms of OS and DFS in the chemotherapy group. Patients with low-risk endocrine receptor-positive breast cancer were included in a study by Thurlimann et al., in which hormone therapy alone and AC (doxorubicin and cyclophosphamide) plus hormonotherapy were compared, and there was no difference in 5-year OS and DFS (p=0.94) [16]. A study conducted by Hee Yonk et al. on patients with early-stage Luminal-A subtype breast cancer found that 5-year DFS (p=0.70) and OS (p=0.483) were similar to those patients who received chemotherapy and those who did not [17]. In this study, lymph node involvement, pathologic T-stage and disease stage were more advanced in the chemotherapy arm, which is similar to the findings of our study.

Axillary lymph node status has an important effect on the prognosis of patients, since those with positive lymph nodes have been shown to present worse prognosis than negative ones [13]. In the present study, there was no difference in terms of OS and DFS in the group receiving taxane-based chemotherapy compared to chemotherapy without taxane. In a study conducted by Kader et al., docetaxel combined with FEC (Fluorouracil, Epirubicin, Cyclophosphamide) chemotherapy in Luminal-A subtype breast cancer patients did not show any difference in 4-year DFS (p=0.83). The CALGB 9344 study demonstrated that treatment with administration of paclitaxel after adjuvant chemotherapy with doxorubicin plus cyclophosphamide was particularly beneficial especially for hormone receptor negative HER2 positive tumors, while Luminal-A tumors displayed a poor benefit [18]. The majority of cases consisted of lymph node positive patients in both the aforementioned studies and the present study. It seems that the addition of taxane treatment does not secure any additional benefit for these patients. Chemotherapy without taxane may be an option, especially for lymph node positive Luminal-A subtype breast cancer patients for whom chemotherapy is recommended.

This study has several limitations. The first limitation is the low number of patients enrolled. As this study was designed retrospectively, unknown intervening factors may have affected the outcomes. In addition, patients receiving chemotherapy had a more advanced disease stage. Similarly, the clinical stage and lymph node involvement were more advanced in patients treated with taxane-based chemotherapy. Another limitation is that we defined Luminal-A-like using IHC. If we

Table 1. Clinical and pathologic characteristics

Characteristics	*Chemotherapy + (n=104) n (%)*	*Chemotherapy – (n=32) n (%)*	*p value*
Age at diagnosis, years			0.843
Median	50	49	
Range	(27-75)	(35-75)	
Menopause situation			0.976
Premenopause	54 (48.1)	15 (46.9)	
Postmenopause	50 (51.9)	16 (50)	
Unknown		1 (3.1)	
T stage			<0.001
pT1	46 (44.2)	26 (81.3)	
pT2	53 (51)	6 (18.8)	
pT3	4 (3.8)		
pT4	1 (1)		
Clinical stage			<0.001
1	18 (17.3)	18 (56.3)	
2	60 (57.7)	13 (40.7)	
3	26 (25)	1 (3.1)	
N stage			0.001
pN0	40 (38.5)	22 (68.8)	
pN1	39 (37.5)	9 (28.1)	
pN2	20 (19.2)	1 (3.1)	
pN3	5 (4.8)		
Histologic grade			<0.001
G1	10 (9.6)	16 (50)	
G2	87 (83.7)	15 (46.9)	
G3	5 (4.8)	1 (3.1)	
Unknown	2 (1.9)		

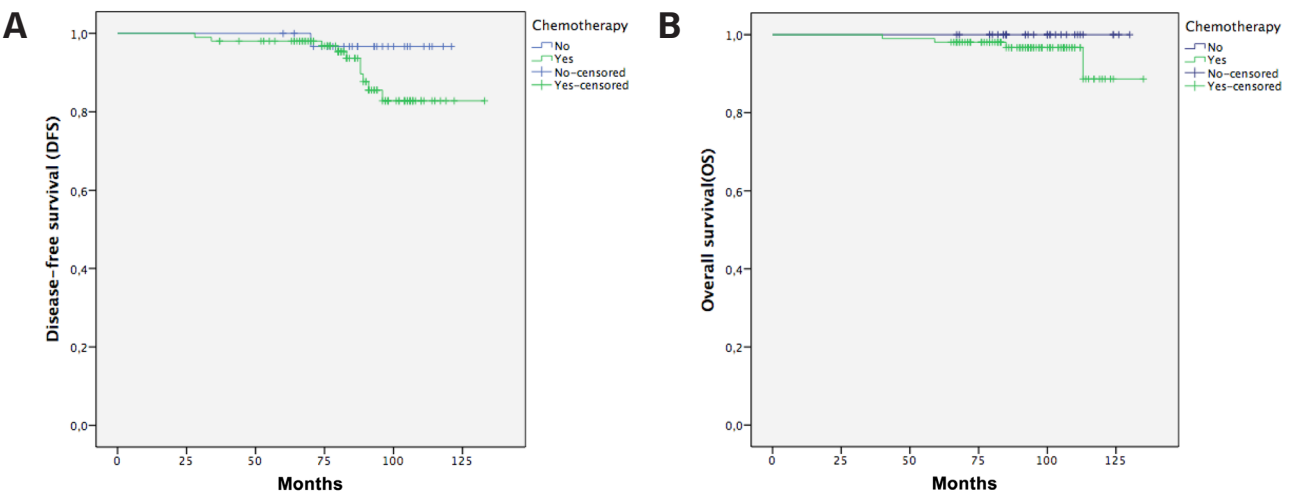

Figure 1. A: 10-year cumulative disease-free survival for the groups with and without chemotherapy (p=0.230). **B:** 10-year cumulative overall survival for the groups with and without chemotherapy (p=0.242).

Table 2. Clinical and pathological characteristics in patients receiving chemotherapy

Characteristics	*Taxane-based chemotherapy (n=43) n (%)*	*Chemotherapy without taxane (n=61) n (%)*	*p value*
Age at diagnosis, years			0.702
Median	52	48	
Range	(27-75)	(35-71)	
Menopause situation			0.599
Premenopause	21 (48.8)	33 (54.1)	
Postmenopause	22(51.2)	28 (45.9)	
T stage			0.343
pT1	17 (39.5)	29 (47.5)	
pT2	23 (53.5)	30 (49.2)	
pT3	2 (4.7)	2 (3.3)	
pT4	1 (2.3)		
Clinical stage			<0.001
1	1 (2.3)	17 (27.9)	
2	20 (46.5)	40 (65.6)	
3	22 (51.2)	4 (6.6)	
N stage			<0.001
pN0	2 (4.7)	38 (62.3)	
pN1	19 (44.2)	20 (32.8)	
pN2	17 (39.5)	3 (4.9)	
pN3	5 (11.6)		
Histologic grade			0.587
G1	3 (7)	7 (11.5)	
G2	36 (83.7)	51 (83.6)	
G3	2 (4.7)	3 (4.9)	
Unknown	2 (4.7)		

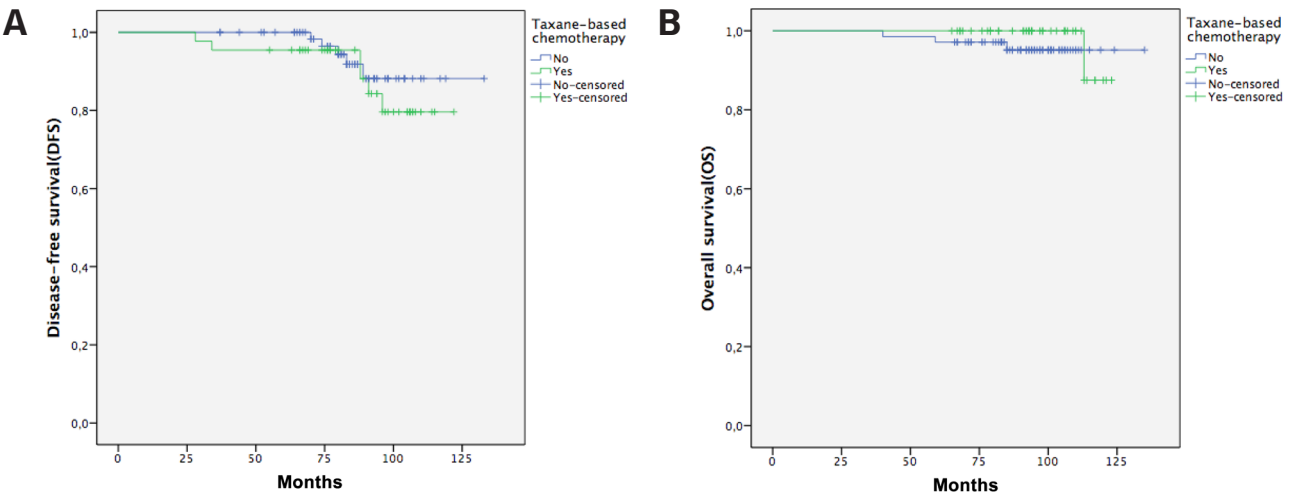

Figure 2. A: 10-year cumulative disease-free survival for the groups that received taxane-based chemotherapy and the one administered taxane-free chemotherapy (p=0.501). **B:** 10-year cumulative overall survival for the groups with and without chemotherapy that received taxane-based chemotherapy and the one administered taxane-free chemotherapy (p=0.391).

could divide patients molecularly into subgroups, some of them may have fallen under the high-risk class.

In conclusion, adjuvant chemotherapy for Luminal-A subtype breast cancer did not demonstrate any benefit in terms of DFS or OS in our study. Also, taxane-based chemotherapy did not secure any benefit for OS and DFS in Luminal-A subtype breast cancer with a relatively more advanced stage and lymph node involvement. In the present study, the efficacy of taxanes was lower than any subtype-containing adjuvant studies. Adjuvant chemotherapy may have little benefit for low-risk node-positive Luminal-A subtype breast cancer. Low-density treatments may be preferred if chemotherapy is being considered for these patients. We believe that chemotherapy is not beneficial in a significant proportion of Luminal-A subtype breast cancer patients. Regarding this subtype, prospective randomized studies with larger cohorts are required in order to determine which patients are more likely to benefit from chemotherapy.

Conflict of interests

The authors declare no conflict of interests.

References

1. Ferlay J, Soerjomataram II, Dikshit R et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. Int J Cancer 2015;136: 359-86.
2. Early Breast Cancer Trialists' Collaborative Group [EBCTCG]. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-717.
3. Group EBCTC. Polychemotherapy for early breast cancer: an overview of the randomised trials. Lancet 1998;352:930-42.
4. Ferguson T, Wilcken N, Vagg R, Ghersi D, Nowak K. Taxanes for adjuvant treatment of early breast cancer. Cochrane Database Syst Rev 2007;11:CD004421.
5. De Laurentis M, Cancello G, D'Agostino D et al. Taxane-based combinations as adjuvant chemotherapy of early breast cancer: A meta-analysis of randomized trials. J Clin Oncol 2008;26:44-53.
6. Hamilton A, Piccart M. The contribution of molecular markers to the prediction of response in the treatment of breast cancer: A review of the literature on HER-2, p53 and BCL-2. Ann Oncol 2000;11:647-63.
7. Bonadonna G, Brusamolino E, Valagussa P et al. Combination chemotherapy as an adjuvant treatment in operable breast cancer. N Engl J Med 1976;294:405-10.
8. Bartlett J, Canney P, Campbell A et al. Selecting Breast Cancer Patients for Chemotherapy: The Opening of the UK OPTIMA Trial. Clin Oncol 2013;25:109-16.
9. Goldhirsch A, Wood WC, Coates AS, Gelber RD, Thürlimann B, Senn HJ. Strategies for subtypes-dealing with the diversity of breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast cancer 2011. Ann Oncol 2011;22:1736-47.
10. Callagy G, Cattaneo E, Daigo Y et al. Molecular classification of breast carcinomas using tissue microarrays. Diagn Mol Pathol 2003;12:27-34.
11. Goldhirsch A, Winer EP, Coates AS et al. Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen international expert consensus on the primary therapy of early breast Cancer 2013. Ann Oncol 2013;24:2206-23.
12. Coates AS, Winer EP, Goldhirsch A et al. Tailoring therapies - improving the management of early breast cancer: St Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2015. Ann Oncol 2015;26:1533-46.
13. Sun Y, Liu X, Cui S et al. The inconsistency of molecular subtypes between primary foci and metastatic axillary lymph nodes in Luminal A breast cancer patients among Chinese women, an indication for chemotherapy? Tumor Biol 2016;37:9555-63.
14. Early Breast Cancer Trialist Group. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 2005;365:1687-1717.
15. Han Y, Li Q, Xu BH et al. Adjuvant chemotherapy may improve survival of patients with luminal A breast cancer and positive lymph nodes. Gen Molec Res 2015;14:8563-73.
16. Thürlimann B, Price KN, Gelber RD et al. Is chemotherapy necessary for premenopausal women with lower-risk node-positive , endocrine responsive breast cancer ? 10-year update of International Breast Cancer Study Group Trial 11-93. Breast Cancer Res Treat 2009;113:137-44.
17. Kwak HY, Chae BJ, Eom YH et al. Is adjuvant chemotherapy omissible in women with T1-2 stage, node-positive, luminal A type breast cancer? J Chemother 2015;27:290-96.
18. Hayes DF, Thor AD, Dressler LG et al. HER2 and Response to Paclitaxel in Node-Positive Breast Cancer. N Engl J Med 2007;357:1496-506.