RESEARCH ARTICLE

Impact of Adjuvant Chemotherapy in Elderly Breast Patients in Taiwan, A Hospital-Based Study

Hsiu Chuan Lee[1], Wei Yu Chen[1,2], Wen Tsung Huang[3], Kuo Chen Cheng[1,4], Yu Feng Tian[5,6], Chung Han Ho[7], Chao Jung Tsao[3], Yin Hsun Feng[1,2,8]*

Abstract

Purpose: Decisions as to whether to provide adjuvant treatment in older breast cancer patients remains challenging. Side effects of chemotherapy have to be weighed against life expectancy, comorbidities, functional status, and frailty. To aid decision-making, we retrospectively analyzed 110 women with breast cancer treated with a curative intention from 2006 to 2012. Survival data with clinical and pathological parameters were evaluated to address the role of adjuvant chemotherapy in this study population. **Method:** A total of 110 elderly (>70 years) patients that received mastectomy at two hospitals in Taiwan were observed retrospectively for a medium of 51 months. After mastectomy, patients received conservative treatment or adjuvant chemotherapy, or hormone therapy following clinical guidelines or physician's preference. Data were collected from the cancer registry system. **Results:** Median age at diagnosis was 75.7 years. Thirty-five percent of patients received adjuvant chemotherapy, these having a significantly younger age (mean=74.0±5.3 vs 77.5±5.3, p<0.001) and higher tumor staging (p=0.003) compared with their non-chemotherapy counterparts. Five-year overall survival was non-significantly higher in patients who received adjuvant chemotherapy (with chemotherapy 64.2% vs without chemotherapy 62.6%, p=0.635), while five-year recurrence free survival was non-significantly lower (with chemotherapy 64.1% vs without chemotherapy 90.5%, p=0.80). **Conclusions:** In this analysis, adjuvant chemotherapy tended to be given to patients with a younger age and higher tumor staging at our institute. It was not associated with any statistically significant improvement in survival and recurrence rate. Until age specific recommendations are available, physicians must use their clinical judgment and assess the tumor biology with the patient's comorbidities to make the best choice. Clinical trials focusing on this critical issue are warranted.

Keywords: Breast cancer- adjuvant chemotherapy- elderly

Introduction

Background

Elderly breast cancer has become an increasingly impotent issue nowadays with increasing proportion of aging people due to decreased birth rate and longer life expectancy as well as western life style globally (Shen et al., 2005). Female breast cancer is the major cause of cancer death among women worldwide from latest 2015 global cancer statistic and it remains to be the leading cause of death in less developed countries. In more developed regions, breast cancer death fall behind lung cancer in 2015 (Torre et al., 2015). This may attribute to the advancement of screen and treatment. However, elderly patient with breast cancer did not improved significantly as in younger population (Bastiaannet et al., 2011). Treatment for elderly breast cancer remains a challenge due to lack of clinical trial and due to fragility and shorter life expectancy among elderly population (Le Saux et al., 2015).

The benefits must be balanced with toxicity and shorter life expectancy in elderly breast cancer treatment. Careful evaluation can be assisted by comprehensive geriatric assessment (GCA), which is the most wildly accepted evaluation tool(Soubeyran et al., 2014). The variability of life expectancy in elderly is very large (Walter and Covinsky, 2001), with the concern that elderly patient had higher chemotherapy related toxicity compared to younger patient (Klepin et al., 2014). Therefore, treatment must be guided by careful evaluation of patient's general condition and treatment plan should be made individually. Currently, the treatment for elderly breast cancer is based on the studies of younger population. Some previous trials attempt to compare the effect of chemotherapy

[1]*Department of Internal Medicine,* [2]*Division of Hematology and Oncology,* [5]*Department of Surgery,* [7]*Department of Medical Research, Chi-Mei Medical Center, Yong Kang,* [3]*Department of Hematology-Oncology, Chi-Mei Medical Center, Liouying,* [4]*Department of Safety Health and Environmental Engineering,* [8]*Department of Nursing, Chung Hwa University of Medical Technology,* [6]*Department of Health and Nutrition, Chia Nan University of Pharmacy and Science, Tainan, Taiwan. *For Correspondence: yinhsun.feng@gmail.com*

with placebo were closed prematurely due to insufficient accrual (Leonard et al., 2011). There are only retrospective studies available to define the treatment, most of them originated from regions other than Asian area(Angarita et al., 2015; Jueckstock et al., 2015).

The difference of breast cancer between young aged population and old aged counterpart has been extensively studied. Tumor tends to be bigger at first diagnosis in elderly patients and most older breast cancer patients suffer from well differentiated tumor with positive hormone receptor status showing typically low metastatic potential associated with comparably good prognosis (Pierga et al., 2004). Almost 20% of tumors found in older patients are hormone receptor negative, but even in triple negative tumors the prognosis improves with patient's age at first diagnosis (Bergen et al., 2016). Regarding the shorter life expectancy and higher comorbidity in aged breast cancer, the life expectancy varied large form person to person within elderly population. Therefore, treatment needs to be individualized according to the performance of the elderly. Comprehensive Geriatric Assessment is recommended to evaluate the benefits and risks of treatment. Considering the risk of chemotherapy side effects, older patients were vulnerable to chemotherapy, more likely to have adverse effect, and received less dose compare to younger patients (Crivellari et al., 2000).

For the reasons above, there is limited treatment that proven effective within elderly population. Surgical treatment followed by adjuvant radiotherapy and hormone therapy can showed some benefits in selected population (Westphal et al., 2016). But for adjuvant chemotherapy, there is limited evident. Most elderly were excluded from the clinical trial and chemotherapy were given in small populations of people and no randomized control trails were included to define the benefit of adjuvant chemotherapy within the selected population. To address the issue of adjuvant chemotherapy of elderly patients with breast cancer focused on Asian population, we will conduct the study in our hospitals.

In this study, we tried to find the outcome of adjuvant chemotherapy for elderly breast cancer based on the retrospective analysis in our institutes. We retrospectively analyzed 110 patient form two hospitals in Taiwan to evaluate the progression free survival and overall survival of the patients who receiving chemotherapy and not receiving chemotherapy in order to help to define the treatment direction for the future.

Materials and Methods

Patient and data collection

Data were collected retrospectively form cancer registry system in two hospitals in Taiwan. Patients underwent either breast conservative surgery or mastectomy between 2006 to 2012 were included in this study. Other inclusion criteria were the first diagnosed age was > 70 years. Patient with male gender and data missing were excluded from the study. For patients who had performance status, defined by Eastern Cooperative Oncology Group, worse than 2.0 were also excluded. Most of these patients had

palliative radiotherapy, hormone therapy or supportive care only. Follow up data were last update till August of 2015. Extract data including

1. Patient and the tumor characteristics such as age, comorbidity and staging.

2. Surgical pathology: pathology stage, grade, hormone receptor, her2 status, invasive and ductal carcinoma in situ.

3. Adjuvant therapy including radiotherapy, chemotherapy, anti-her2 treatment (trastuzumab in all cases) and hormone therapy given.

4. Outcome was recorded as progression free survival and overall survival.

5. Surveillance information including date of last visit to oncology department, date of recurrence, loss of follow up. Date of diagnosis was defined as date for biopsy proven disease.

Tumor histopathology

Tumor samples were harvested after surgical resection for primary breast cancer and pathology was classified according to the world health organization (WHO) tumor classification. Staging was according to the American joint committee on cancer (AJCC) edition at the time of diagnosis. The definitions of estrogen/ progesterone receptor (ER/PR) positivity were defined as 1.0%/5.0% of tumor cells showed nuclear staining. Her-2 were considered positive with immunohistochemistry staining of 3+, in 2+ with additional reflex fluorescence in situ hybridization (FISH) was performed and showed a positive result. 0 or 1+ station or 2+ staining with FISH negative result were considered Her-2 negative.

Definition of comorbidities

The comorbidities were evaluated by medical record and clinical data. The laboratory diagnosis of diabetes mellitus based on any one of the following tests: HbA1C >= 6.5%, fasting plasma glucose level >= 126 mg/dL, oral glucose tolerance test >= 200 mg/dL. The diagnosis of hypertension was documented when blood pressure reading was consistently 140/90 mmHg or above. Clinically, heart failure can be diagnosed by ejection fraction < 50% from echocardiography for systolic heart failure or impaired left ventricular relaxation for diastolic heart failure. Otherwise, the clinical diagnosis of liver cirrhosis derived from image report of cirrhosis and stage three or severe of chronic kidney disease was included as comorbidity in our study which represent as estimated glomerular filtration rate less than 60 ml/min.

Statistics

The mean (standard deviation) and frequency (percentage) were presented as continuous variables and discrete variables, respectively. Pearson's Chi square test or Student's t-test was used to evaluate the continuous variables and discrete variables difference between with and without chemotherapy, respectively. For overall survival and disease free survival, Kaplan-Meier method was adapted for survival curve with log-rank test for estimating the difference. Cox regression model was used to compare the individual parameters with respect
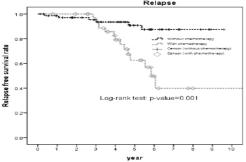
Figure 1. Relapse Free Survival According to Adjuvant Chemotherapy)

Figure 2. Overall Survival According to Adjuvant Chemotherapy

to survival. All statistical analyses were performed with SPSS statistical software (version 17, SPSS Inc, Chicago, IL). Significance were set as p<0.05.

Results

A total of 110 women met the inclusion criteria with median age at diagnosis of 75.7 years were collected. The mean follow up period was 51months. Lost follow up rate was 8.0%. Patients were divided into patient without adjuvant chemotherapy and with adjuvant chemotherapy. We compared the baseline data of the patient (Table 1 and Table 2). There were 39.0 patients receive adjuvant chemotherapy and 71 patients without chemotherapy after surgery. In comparison with no-chemotherapy group, patients who received chemotherapy were significant younger age (mean=74 vs77.5, p<0.001) and higher tumor stage (p<0.001). Her2 receptor and hormone receptor had no significant difference as well as comorbidity. Up to 12% of patients had no information of exact her2 status and relatively low percentage (5%) of triple negative
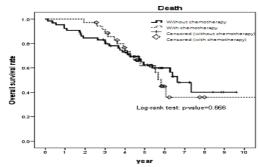
breast cancer was identified in our study. The impact of triple negative breast cancer can not be investigated extensively here.

Aside from the adjuvant chemotherapy, both groups received similar treatment as standard of care. Both groups received hormone therapy of similar proportion (with chemotherapy 79.5% and without chemotherapy 73.2%). We also evaluated the different chemotherapy regimens that were given to the patients. Among 39 patients who received adjuvant chemotherapy, 23 (59%) patients received adjuvant chemotherapy with CMF, 8 (20.5%) patients received adjuvant chemotherapy with anthracycline based regimen, 8(20.5%) patients received adjuvant chemotherapy with anthracycline and taxane based regimen. No treatment related mortality was yielded. Outcome was presented as progression free survival and overall survival by Kaplan-Meier plots. Patients who received chemotherapy had significantly lower relapse free survival (p>0.001) (Figure 1). The five years relapse free survival is 64% in chemotherapy group and 90% in without chemotherapy group. Patients who

Table 1.The Demographic Parameters Categorized by Adjuvant Chemotherapy

	Without adj C/T	With adj C/T	All	P-value
Patient No.	71 (64.5)	39 (35.5%)	110	
Age (mean, range)	77.5±5.3	74±3.0		<0.001
Age				
70-74	24 (33.8%)	24 (61.5%)	48	0.003
75-79	25 (35.2%)	14 (35.9%)	39	
80-84	14 (19.7%)	1 (2.6%)	15	
85~	8 (11.3%)	0 (0.0%)	8	
Stage				
I	25 (35.2%)	5 (12.8%)	30	<0.001
II	34 (47.9%)	12 (30.8%)	46	
III	12 (16.9%)	22 (56.4%)	34	
Hormone receptor				
Pos	55 (77.5%)	27 (69.2%)	82	0.343
Neg	16 (22.5%)	12 (30.8%)	28	
Her2 receptor				
Pos	19 (26.8%)	9 (23.1%)	28	0.055
Neg	40 (56.3%)	29 (74.4%)	69	
Unknown	12 (16.9%)	1 (2.6%)	13	
Triple negative	3 (4.2%)	2 (6.5%)	5	1.000

Table 2. The Hormone Therapy and Comorbidity Categorized by Adjuvant Chemotherapy

	Without adj C/T	With adj C/T	All	P-value
Hormone therapy	52 (73.2%)	31 (79.5%)	83	0.466
Non Hormone therapy	19 (26.8%)	8 (20.5%)	27	
Anti-her-2 therapy	1 (1.4%)	4 (12.9%)	5	1.000
Comorbidity (DM/HTN/CHF/Cirrhosis/renal failure)	53 (74.6%)	26 (66.7%)	79	0.373
DM	22 (31.0%)	14 (35.9%)	36	0.599
HTN	45 (63.4%)	22 (56.4%)	67	0.474
CHF	5 (7.0%)	2 (5.1%)	7	1.000
Cirrhosis	4 (5.6%)	3 (7.7%)	7	0.697
CKD	6 (8.5%)	3 (7.7%)	9	1.000

Table 3. The Univariate and Multivariate Study of Tumor Relapse

		Univariate		Multivariate	
		HR(95%CI)	P-value	HR (95%CI)	P-value
adj C/T	yes	4.5(1.7-11.8)	0.002	2.1 (0.6-7.5)	0.28
	no	Ref.		Ref.	
Age	70-74	Ref.		Ref.	
	75-79	1.1 (0.4-2.6)	0.910	1.1 (0.4-3.2)	0.81
	80-84	0.0	0.974	-	-
	85~	1.1 (0.1-8.7)	0.921	1.7 (0.1-23.6)	0.708
Stage	I	Ref.		Ref.	
	II	2.1 (0.4-10.2)	0.379	0.9 (0.2-5.3)	0.98
	III	7.4 (1.7-33.3)	0.009	4.6 (0.8-25.7)	0.084
Hormone receptor	Pos	0.4 (0.2-0.9)	0.024	0.2 (0.1-0.81)	0.024
	Neg	Ref.		Ref.	
Her2 receptor	Pos	1.6 (0.6-4.1)	0.336	2.1 (0.7-6.1)	0.181
	Neg	Ref.		Ref.	
Unknown		0.9 (0.2-4.7)	0.956	1.8 (0.3-11.7)	0.552
Hormone therapy	Yes	1.1 (0.4-3.4)	0.836	2.7 (0.6-12.7)	0.194
	No	Ref.		Ref.	
DM	(yes vs. no)	0.6 (0.3-2.1)	0.644	0.6 (0.2-2.2)	0.452
HTN	(yes vs. no)	0.5 (0.2-1.3)	0.16	0.3 (0.1-1.1)	0.063
CHF	(yes vs. no)	0.1 (0.00-65.6)	0.402	-	-
Cirrhosis	(yes vs. no)	0.1 (0.00-201.4)	0.471		-
CKD	(yes vs. no)	0.6 (0.1-4.2)	0.573	0.9 (0.1-9.3)	0.967

received chemotherapy had insignificantly shorter overall survival (p=0.666) (Figure 2). The overall survival at five years was 64% with chemotherapy and 62% in without chemotherapy group. The overall survival were higher in chemotherapy group in initial five years, but the survival crossover and became inferior to non-chemotherapy group after 5.0 years that reflects the higher recurrence rate in chemotherapy group despite aggressive adjuvant chemotherapy in more advanced cancer status.

We evaluated the multivariate and univariate study for the cause of death and relapse (Hazard ratio (HR) of death were calculated at the end point of ten years, loss follow up patient rate were 8%). In the all causes of relapse, patients who of higher tumor staging and patients who received chemotherapy had significantly higher tumor relapse rate. HR of relapse in stage III breast cancer is 7.4 (p=0.009) in univariate study and 4.6 (p=0.084) in multivariate study. HR of relapse for patient who received chemotherapy were 4.2 (p=0.002) in univariate study and 2.1 (p=0.280) in multivariate study. The good predictor factors for relapse free survival were hormone receptors. Patients who were hormone receptors positive had lower tumor relapse, HR=0.4 (p=0.024) in univariate study and HR=0.02 (p=0.024) in multivariate study (Table 3).

We analyzed the cause of death with multivariate and univariate analysis. Patients of Age >85 or stage III tumor have significant higher hazard ratio of death both in univariate and multivariate analysis (age >85: HR=9.3 p<0.001 in univariate analysis and HR=18.0 p<0.001 in multivariate analysis, Stage III: HR=4.2 p=0.002 in

Table 4.The Univariate and Multivariate Study of Death.

		Univariate		Multivariate	
		HR (95%CI)	P-value	HR (95%CI)	P-value
adj C/T	yes	1.2 (0.6-2.1)	0.666	0.9 (0.3-2.4)	0.794
	no	Ref.		Ref.	
Age	70-74	Ref.		Ref.	
	75-79	1.2 (0.6-2.5)	0.702	1.1 (0.5-2.6)	0.795
	80-84	1.7 (0.7-4.1)	0.205	3.4 (1.2-9.6)	0.019
	85~	9.3 (3.6-23.6)	<0.001	18.1 (5.1-64.6)	0.000
Stage	I	Ref.		Ref.	
	II	1.8 (0.7-4.5)	0.229	1.4 (0.5-3.8)	0.575
	III	4.2 (1.7-10.6)	0.002	6.5 (2.1-20.2)	0.001
Hormone receptor	Pos	1.1 (0.5-2.2)	0.877	0.5 (0.2-1.6)	0.264
	Neg	Ref.		Ref.	
Her2 receptor	Pos	1.4(0.8-2.8)	0.266	1.7 (0.8-3.7)	0.160
	Neg	Ref.		Ref.	
	Unknown	1.4 (0.5-3.7)	0.5	1.5 (0.5-4.8)	0.523
Hormone therapy	Yes	1.6 (0.7-3.6)	0.265	3.5 (1.0-11.8)	0.045
	No	Ref.		Ref.	
DM	(yes vs. no)	1.0 (0.5-1.9)	0.945	1.0 (0.5-2.1)	0.944
HTN	(yes vs. no)	0.6(0.3-1.1)	0.118	0.3 (0.2-0.8)	0.008
CHF	(yes vs. no)	1.9 (0.7-4.9)	0.176	1.9 (0.6-6.7)	0.285
Cirrhosis	(yes vs. no)	1.41 (0.43-4.56)	0.571	0.7 (0.14-3.05)	0.592
CKD	(yes vs. no)	1.2 (0.4-3.5)	0.674	1.7 (0.5-5.9)	0.402

univariate analysis and HR=6.5 p=0.001 in multivariate analysis). Patients with hormone receptor positive showed improved HR (0.5) of death but no significance was reached (p=0.264). Patients who received hormone therapy had significantly increased risk of death noted in multivariate analysis (HR=3.5, p=0.045). Univariate analysis also showed increased risk of death by hormone therapy but no significance was identified (HR=1.6, p=0.265) (Table 4).

Discussion

In this retrospective database analysis of elderly and surgically treated breast cancer patients, we showed that it failed to demonstrate significant benefits for patients who received adjuvant chemotherapy after surgery. In general consideration for adjuvant chemotherapy in elderly patients, it is likely to deliver the potential toxic treatment to patients with younger age and advanced cancer stage. And in this group without adjuvant chemotherapy, the patients had longer progression free survival partially because of less advanced stage with clinical judgement from clinical physicians. In most studies reported previously, only small proportion of elderly with good performance status and few comorbidity received chemotherapy (Angarita et al., 2015). As a result, physicians tended to be more conservative in elderly breast cancer.

In our report, as high as 37% of elderly patients received chemotherapy. The patients were more aggressively treated with chemotherapy compare to other study as around 10% (Giordano et al., 2006; Jueckstock et al., 2015). However, the survival of chemotherapy group was not inferior to without chemotherapy group. A large population based study using Surveillance, Epidemiology, and End Results Program-Medicare and Texas Cancer Registry-Medicare databases disclosed that 2.9% of patients with age older than 66 years treated with adjuvant chemotherapy for early breast cancer died within one year after diagnosis. Older age and higher comorbidity index were associated with the increased risk of short-term mortality (Rosenstock et al., 2016). The safety of adjuvant chemotherapy in elder women remains an important task. A retrospective study focused on anthracycline-contained adjuvant chemotherapy in elderly women with early breast cancer rose the concern of increased hematological toxicity and relatively lower dose intensity in elderly patients while comparing with the younger (Karavasilis et al., 2016). Another population based and observational cohort study predicted that adjuvant chemotherapy was associated with a mortality reduction of approximately 15.0% in older women with hormone receptor-negative breast cancer (Elkin et al., 2006). In fact, the short term survival was superior in chemotherapy group which reflected the potential effect of chemotherapy on tumor recurrence. For the concern of safety of cytotoxic therapy, there is no increase in chemotherapy related short term mortality and complication despite higher rate of elderly receiving chemotherapy in our study. It reflected that the adjuvant chemotherapy in elderly breast cancer was well tolerant and aging status should not be considered as a great barrier to prevent patients away from adjuvant

treatment.

Currently there is emerging data that support the benefits of chemotherapy in early stage elderly breast cancer. In one randomized controlled study, patient who receive chemotherapy had improved survival, especially in the hormone negative group (Muss et al., 2009). The benefits of chemotherapy in younger patients with hormone negative and lymph node positive had been well established in meta-analyzed study (Early Breast Cancer Trialists' Collaborative et al., 2012). For elderly patient similar phenomenon can be seen in a large retrospective study (Giordano et al., 2006). However, in our study, we do not provide enough evidence to support the benefit of adjuvant chemotherapy. This is probably due to the limitation of our study with small sample size, inadequate for subgroup analysis and relatively older age in our study of Asian population. That makes the potential benefits not easily observed.

Breast cancer with positive hormone receptor was considered as a good prognosis factor and hormone therapy shall be given accordingly. In our study, we conducted the multivariant and univariant analysis to correlate survival with clinical and pathological parameters. The results showed the patient with hormone receptor positive had improved relapse free survival. According to the guideline of the International Society of Geriatric Oncology and European Society of Breast Cancer Specialists, hormone therapy is generally recommended for the patient with hormone receptor positive elderly breast cancer. The effect of hormone therapy were comparable with younger breast cancer patients (Biganzoli et al., 2012; Wildiers et al., 2007).However, in our study, benefits did not see in overall survival. This may be due to the relatively old age and high comorbidity that patients often died from non-cancer cause.

Adjuvant chemotherapy did not associated with improved overall survival, and was associated with non-significantly lower progression free survival in our study. But we can realize that it is important to understand the current status of adjuvant chemotherapy of elderly breast cancer in real world practice, especially in Asian population, although the limitation of our study derived from the fact that the study was retrospective with relative small population. For aging society, well designed randomized control trials were needed to help the decision making of elderly breast cancer treatment.

This study showed there were no benefits of overall survival or disease free survival identified for elderly breast cancer to receive adjuvant chemotherapy currently. This may be due to the limitation of the study, non-randomized and retrospective manner. The treatment –related mortality in adjuvant chemotherapy group was not significantly higher compared with non-adjuvant chemotherapy counterpart. Since medical trial has been explored into old aged patients to meet the clinical demands. But it remains a challenge in elderly patient with the reason of frail status. Our results raised the potential choice of adjuvant chemotherapy in Asian elderly with early breast cancer. The safety was confirmed in our study but the effectiveness remains unresolved answer and well-defined randomized

trials are required to answer this puzzle. Despite significant advance in breast cancer treatment, the most appropriate management for elderly patients is unknown as the safety, effectiveness and necessity of different therapeutic remain under-studied in this population. Until data are available to develop age specific recommendations, physician will have to depend largely on experience and patient's condition and patient's willing to make the best choice for the patient individually.

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