

*Research Article***Outcome of Adjuvant 6 Cycles Chemotherapy versus 8 Cycles In Breast Cancer****El Sayed M. Ali, Emad Eldin N. Hassan and Heba A. Elsaygheer Abdelal**

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Abstract

Background: Breast cancer is the most common site-specific cancer in women, the second most common cancer in the world, and is the leading cause of death from cancer for women aged 20 to 59 years. **Aim of the study:** To compare the results of disease-free survival (DFS), overall survival (OS), and toxicity level on both arms of patient who received 3 cycles of Anthracyclines followed by 3 cycles of Taxanes versus 4 cycles of Anthracyclines followed by 4 cycles of Taxanes. **Patient and Method:** A sample of 301 breast cancer patients of the oncology department of Sohag University Hospital, Sohag Cancer Center and clinical oncology clinic of Sohag Health Insurance participated in the study. Descriptive, significant tests and comparative statistical techniques were employed. **Results:** 62% of patients were postmenopausal and 37% premenopausal. 50.8% of patients received 6 cycles chemotherapy and 49.2 % received 8 cycles Radiotherapy was administered to 99.3% patients and hormonal therapy was given to 87.4% patient. 18 cases of patients developed metastasis or locoregional recurrence. The 5yr OS of the whole patients is 92.2% and 91.9% for 6-cycles and 8-cycles arms respectively with no significant effect of the number of chemotherapy cycles on OS with P-value 0.5. The 5yr DFS of the whole cohort of patients is 96.1%, 91.1% respectively, for 6 and 8-cycles chemotherapy with no significant impact of the number of chemotherapy cycles and (P-value 0.2). **Conclusion:** Eight cycles (4 taxanes and 4 anthracyclines) is not superior to 6 cycles (3 taxanes and 3 anthracyclines) as there is no statistical significance between both arm with increased incidence of toxicity with longer treatment duration.

Key Words: breast cancer, chemotherapy toxicity, number of chemotherapy cycles, survival rate.

Introduction

Breast cancer is the most common site-specific cancer in women and is the second most common cancer in the world, and is the leading cause of death from cancer for women aged 20 to 59 years⁽¹⁾. Breast cancer is sometimes found after symptoms appear, but many women with early breast cancer have no symptoms. The most common symptom of breast cancer is a new lump or mass which is painless, hard and has irregular edges, but breast cancers can be tender, soft, rounded or even be painful. For this reason, it is important to put any new breast mass or lump or breast change into consideration. The increasingly early detection of breast cancer has resulted in significant improvements in the rate of cure in this disease. Increase patient awareness of the nature of the disease and self-examination with the availability and applicability of recent diagnostic modalities can significantly decrease the morbidity and mortality of breast cancer. Breast self-examination, screening mammogram with

complementary US and MRI when needed remains the cornerstone in any screening program. Treatment of breast cancer requires a wise judgment and intervention of a breast surgeon, medical oncologist, and radiotherapist.

Aim of the work:

In this study, we compare the results of disease-free survival (DFS), overall survival (OS), and toxicity level on both arms of the patient who received 3 cycles of Anthracyclines followed by 3 cycles of Taxanes versus 4 cycles of Anthracyclines followed by 4 cycles of Taxanes.

Materials and Method

Study design: A retrospective study was conducted at Sohag University Hospital, Sohag Cancer Center and health insurance who presented from 2010 till 2017.

Study settings and patients: A sample of 301 patients from both hospitals participated in the study. The inclusion criteria for patients were breast cancer female patients of any age, Stages

(II, III) breast cancer, any histological type of breast cancer and all grades of breast cancer. Patients who were Stage (I) breast cancer, metastatic breast cancer (MBC), recurrent breast cancer and patients with co-morbidities that contraindicate chemotherapy were excluded from the study.

Study tools: The data were collected in an excel worksheet. Factors investigated in this study include age, menopausal status, estrogen, and progesterone receptor, human epidermal growth factor receptor 2 status, lymph node status, tumor size, tumor grade, with pathological data registered in patient's file. Receptors' status was determined via the patient's pathological report following primary tumor biopsy. Her2 was determined using the IHC test. All patients underwent surgery MRM or BCS and received postoperative chemotherapy (six or eight cycles), radiotherapy and hormonal treatment according to the hormonal receptor and menopausal state.

Disease-free survival (DFS) was defined as the time interval between curative surgery and the appearance of distant metastasis or local recurrence. Overall survival(OS) was defined as the time interval between the first diagnosis till death or the last time of follow up. Statistical data revealed the relation between chemotherapy cycles number to DFS and OS.

Data analysis: Data were analyzed using SPSS version 20 Quantitative data were represented as mean, standard deviation, median, and range. Qualitative data were presented as numbers and percentages. Survival analysis was done using the Kaplan-Meier method and a comparison

between two survival curves was done using the log-rank test. Graphs were produced by using Excel or SPSS program. P-value was considered significant if it was less than 0.05

Results

This study included 301 patients of breast cancer who were fulfilling our eligibility criteria were included in our study, the follow-up period ranged between periods from February 2010 till August 2018. The median age of patients was 49.7 years (range: 21-79 years). 62% of patients were postmenopausal and 37% premenopausal as in table (1). The most common pathology was IDC constituting 96% of cases. 85.7%, 78.4%, and 20.3 % were ER, PR, and HER2 positive respectively table (2). The most common tumor stage in our study is T2 as in table (3). 19.6% patients underwent breast-conserving surgery, 80.4 % underwent modified radical mastectomy. 50.8% of patient received 6 cycles chemotherapy and 49.2 % received 8 cycles. Radiotherapy was administered to 99.3% patients and hormonal therapy was given to 87.4% patient. 18 cases of patients developed metastasis or locoregional recurrence table. Toxicity was fulfilled in table (4,5,6).

Outcomes of treatment at the end of the study were summarized in tables (7). The 5yr OS of the whole cohort of patients is 92.2% and 91.9% for 6- cycles and 8- cycles arms respectively with no significant effect of the number of chemotherapy cycles on OS with P-value 0.5. The 5yr DFS of the whole cohort of patients is 96.1%, 91.1% respectively, for 6 and 8- cycles chemotherapy with no significant impact of the number of chemotherapy cycles and (P-value 0.2).

Table (1): Demonstrates the patient characteristics

Item		No.	%
Age, years	Before 40	47	15.6
	After 40	254	84.4
Menopausal state	Pre	114	37.9
	Post	187	62.1

Table (1): demonstrates that 62.1% are post-menopausal state

Table (2): Demonstrates the Tumor characteristics

	Frequency	Percent
Pathological stages		
In situ	2	0.70
Invasive ductal	289	96.00
Invasive lobular	8	2.70
Mucinous	1	0.30
Comedo	1	0.30
Grading		
1	20	6.60
2	229	76.10
3	48	15.90
Estrogen receptors		
Negative	43	14.30
Positive	258	85.70
Progesterone receptors		
Negative	65	21.60
Positive	236	78.40
HER		
Negative	225	74.80
Positive	61	20.30
Equivocal	1	0.30
Not assessed	14	4.70

Table (2): demonstrates that the characters of the patient tumors as follow 96.00% of the tumors are invasive ductal carcinoma, 76.1% are grade 2, 85.7% have positive estrogen receptors, 78.4% have positive progesterone receptors and 74.8% have negative HUMAN EPIDERMAL RECEPTORS.

Table (3): Demonstrates the tumor stages

	Frequency	Percent
Tumor staging		
1	22	7.30
2	178	59.10
3	99	32.80
X	2	0.66
Lymph node		
1	59	29.60
2	123	40.90
3	89	29.50

Table (3): demonstrates that the tumor stages as follow 59.1% of the patients has tumor stage 2 and 40.9% of the patients has lymph node 2.

Table (4): shows the distribution of blood cell toxicity in relation to the number of cycles received by the patients

Blood toxicity	Cycles				P value
	6 cycles		8 cycles		
	No	%	No	%	
Neutropenia					0.185
G0	52	33.90	61	41.21	
G1	49	32.00	30	20.27	
G2	28	18.30	32	21.62	
G3	19	12.41	22	14.86	
G4	5	3.26	3	2.20	
Anemia					0.031
G0	38	24.83	33	22.29	
G1	10	6.53	24	16.21	
G2	86	56.20	64	43.24	
G3	12	7.80	17	11.48	
G4	7	4.57	10	6.75	
Thrombocytopenia					.671
G0	122	79.73	131	88.51	
G1	16	10.45	8	5.40	
G2	8	5.22	4	2.70	
G3	6	3.93	5	3.37	
G4	1	0.65	0	0.00	

Table (4): illustrates that the blood toxicity in relation to number of cycles in which 33.9% of the patients whose received 6 cycle had grade 0 neutropenia compared with 41.21% received 8 cycle the difference is statistical insignificant. Also, 56.2 % of the patients whose received 6 cycle had grade 2 Anemia compared with 43.23% received 8 cycle the difference is statistically significant. On the other hand, 79.73 % of the patients whose received 6 cycle had grade 0 Thrombocytopenia compared with 88.51% received 8 cycle the difference is statistically insignificant.

Table (5): shows the distribution of GIT toxicity in relation to the number of cycles received by the patients

GIT	Cycles				P value
	6 cycles		8 cycles		
	No	%	No	%	
Nausea					.873
G1	73	47.71	74	50.00	
G2	62	40.52	59	39.86	
G3	18	11.76	15	10.13	
Diarrhea					.005
G0	105	81.62	110	73.32	
G1	41	14.79	21	26.18	
G2	7	4.57	17	11.48	
Vomiting					.109
G1	79	51.63	60	40.54	
G2	62	40.52	63	42.56	
G3	11	7.18	23	15.54	
G4	1	0.65	2	1.35	

Table (5): illustrates that the GIT toxicity in relation to number of cycles in which 47.71% of the patients whose received 6 cycle had grade 1 nausea compared with 50,00% received 8 cycle the difference is statistical insignificant. Also, 81.62% of the patients whose received 6 cycle had grade 0diarrhea compared with 73.32% received 8 cycle the difference is statistically significant. On the

other hand, 51.63% of the patients who received 6 cycles had grade I vomiting compared with 40.54% who received 8 cycles the difference is statistically insignificant.

Table (6): shows the distribution of neurological and cardiac toxicities in relation to the number of cycles received by the patients

Neurological	Cycles				P value
	6 cycles		8 cycles		
	No	%	No	%	
Parathesia					.555
G0	140	91.50	130	87.83	
G1	10	6.53	13	8.49	
G2	3	1.96	5	3.37	
Cardiac function					0.547
G0	145	94.77	140	94.59	
G1	8	5.22	8	5.40	

Table (6): illustrates that the neurological and cardiac toxicity in relation to number of cycles in which 91.5% of the patients who received 6 cycles had neurological toxicity in the form of parathesia G0 compared with 87.83% who received 8 cycles the difference is statistically insignificant. On the other hand, 94.77% of the patients who received 6 cycles had cardiac toxicity G0 compared with 94.59% who received 8 cycles the difference is statistically insignificant.

Table (7): shows the effect of the number of cycles on the recurrence and survival rates

	6 cycle		8 cycle		P value
	No	%	No	%	
Recurrence state					.288
No recurrence	147	96.10	136	91.10	
Early	5	3.30	9	6.10	
Late	1	0.70	3	2.00	
Survival					.550
Less than or equal five year	141	92.20	136	91.90	
More than five year	12	7.80	12	8.10	

Table (7): illustrates that the recurrence state and five-year survival rate among patients who received 6 cycles versus 8 cycles in which 96.10% of the patients who received 6 cycles had no recurrence compared with 91.10% who received 8 cycles the difference is statistically insignificant. On the other hand, 92.20% of the patients who received 6 cycles had less than or equal five-year survival compared with 91.90% who received 8 cycles the difference is statistically insignificant.

Discussion

Breast cancer is the most common cause of cancer and cancer death worldwide⁽²⁾. Adjuvant chemotherapy in early breast cancer decreases the risks of recurrence and breast cancer mortality⁽³⁾.

In this retrospective study, 301 patients with breast cancer presented to the clinical oncology department in Suhag University Hospital, all received adjuvant chemotherapy sequential anthracycline followed by taxanes. Several

epidemiological and clinical factors were studied as well as prognostic factors influencing local tumor control, distant disease failure in addition to survival.

Chemotherapy reduced the risk of death due to invasive breast cancers by between 7% and 33% in randomized trials and large meta-analyses; this varied according to tumor characteristics, patient age, and the type and duration of treatment⁽⁴⁾. Chemotherapy is the standard of care for women with node-positive

cancer or with a tumor larger than 1 cm⁽⁵⁾. In (Héry C, et al., 2008) trial most of the patients in this trial are post menopause between 50 and 65 years of age. In our study 62.1% are post menopause with a median age of patient 49.7 years⁽⁶⁾. In Hammond ME, et al., 2010 study showed approximately 75% of all breast cancers show positive receptors⁽⁷⁾. In our study, 85.7% show positive ER receptors, 78.4% show positive PR receptors. About 25% of all breast cancers show positive HER-2 gene⁽⁸⁾. In our study, 20.3% of patients show positive expression of HER 2 gene.

In the EBCTC meta-analyses involving taxane-based or anthracycline-based regimens, proportional reductions in risk of recurrence associated with adjuvant chemotherapy were little affected by age, nodal status, tumor diameter or grade, ER expression, and breast cancer mortality was reduced on average by one-third⁽⁹⁾. The CALGB 9344 study that also employed show no survival benefits in HR-positive patients than those with HR- negative patients⁽¹⁰⁾. In our study 5 years survival in HR-positive 91.6% versus 94.7% in HR- negative patient with P-value =0.39. (PACS-01 trial) show patients with 1-3 positive nodes had better DFS in subgroup analyses⁽⁹⁾ also in (GEICAM-9906 trial) benefit was accompanied by an increase of 9.5% vs. 5.1%. DFS depends on the number of positive LNs and tumor size⁽¹¹⁾. In our study DFS is better in a patient with 1-3 positive LN 96.6%, the most common tumor stage is T2 with no significant difference in recurrence or survival. Also, it was better with HER2 negative patients and patients with ER-positive tumors based on subgroup analyses of this trial. In our study DFS for HER 2 negative 93.3% and 95% for HER2 positive with P-value = 0.9, also 5 year survival for ER-negative 94.7% and 91.6% for ER-positive with p = 0.3.

In our study, there were two arms of the patient who received three or four anthracycline-based regimens followed by three or four cycles taxanes respectively to compare superiority of 8 cycles over 6 cycles.

In the United States the standard of treatment is 4 cycles of AC as there is no benefits was found for prolongation of the chemotherapy duration and longer treatment durations was associated with increased toxicity specially cardiac

toxicity⁽¹²⁾. However, the treatment duration still questionable as the studies is insufficient to rule out this. There is many trials was done to compare longer treatment duration one of them is (CALGB) 40101 trial, this trial aim is to compare six cycles of chemotherapy versus four cycles and the results of this study show no significance for longer duration of treatment^{(18),(9)}. In (Shulman LN, et al., 2012) the aim of the study is comparing the superiority of 6 cycles of FEC 100 versus four cycles and the results show no difference in DFS and OS⁽¹³⁾.

NSABP B-36 phase III trial, the aim of this trial is to show benefits from longer chemotherapy duration on DFS this study compared six cycles of (FEC) with four cycles of AC, both given every 3 weeks as adjuvant therapy in patients with node-negative breast cancer. The results of this study show no statistical significance in DFS, OS inpatient receiving 6 FEC versus those receiving 4 cycles AC⁽²⁰⁾.

The outcome of our study revealed that there is no superiority of 8 cycles chemotherapy over 6 cycles as DFS 96% vs 91% for 6 cycles vs 8 cycles respectively with p =0.2. 5 year OS 92% vs 91.9 % for 6 cycle vs 8 cycles respectively with p=0.5. with an increased incidence of toxicity from chemotherapy with longer treatment duration. However, in (Fumoleau P, et al., 1999) study patients' number in this study was 621 with node positive divided into two groups one of them received six cycles of FEC and other group received 3 cycles of same regimen the results of this study show improved DFS and OS for those receiving six cycles⁽¹⁴⁾.

Most non hematologic toxicities were seen with both taxanes and anthracyclines but it was more severe with anthracycline than with taxane, including nausea 32% for the AC line versus 3% with taxane, vomiting (27% versus 1%), and stomatitis (10% v 1%)⁽¹¹⁾. In our study show Vomiting grade III 7% versus 15.5 %, Grade IV vomiting 0.06% versus 0.01% for 6 versus 8 cycles respectively, Grade II diarrhea 4% in 6 cycles versus 11.4% in 8 cycles with p=0.005. Neurological toxicity was more obvious with taxane about 15% developed moderate paresthesis and 3% show sever neurotoxicity only 1 patient have permanent⁽¹⁵⁾. In our study show, 10.5% of patients developed

paresthesia 4% with 6 cycles and 6.5 % with 8 cycles neurotoxicity more evident with taxanes. In CALGB 40101 study, show 3.754 patients who developed toxicity during treatment. The most non hematological toxicity is neuropathy and more evident with taxane arm than with anthracycline 12% with 6 cycles versus 5% with 4 cycles. In NSABP B-36 higher toxicity was more with FEC regimen especially higher grades (grade 3-4 neutropenia, cardiac toxicity and anemia)⁽²¹⁾. In our study high grades of hematological toxicity more with 8 cycles (neutropenia GIII 12.4% v 14.8% with 6 cycles and 8 cycles respectively, anemia GIII 7.8% v 11.4 G IV 4% v 6% for 6 cycles and 8 cycles respectively with $p=0,03$. Cardiac toxicity includes congestive heart failure, arrhythmia, abnormalities in ejection fraction and other cardiac symptoms was about 2% of patients⁽¹⁶⁾. In our study, only 2% developed cardiac toxicity.

The incidence of recurrence in breast cancer patient receiving taxanes or anthracycline regimen is not dependant on age, tumour size, stage, tumour grade and differentiation, nodal sate and hormonal state⁽¹⁷⁾. This study has demonstrated that tumor character (stage ($P=0.3$), pathology type ($P=0.9$), differentiation ($P=0.7$), ER ($p=0.2$), HER-2 ($p=0.9$), patient age ($p=0.3$) or number of chemotherapy cycles ($p=0.2$) have no significant relation with DFS and OS.

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