RESEARCH ARTICLE

Phase II Study of Compliance and Morbidity with 4 Cycles of Taxotere Followed by 4 of Doxorubicin-Cyclophosphamide for Adjuvant Treatment of Operable Breast Cancer Patients

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Abstract

Background: In the adjuvant treatment of breast cancer, anthracycline and taxane based regimens can be used concomitantly or sequentially. The best order in the sequential regimens has yet to be well established. This study evaluated the feasibility of 4 cycles of adjuvant taxotere (100mg/m^2) every 3 weeks followed by 4 cycles of doxorubicin (60 mg/m^2) and cyclophosphamide (600mg/m^2) every 3 weeks. The primary outcome was the safety profile. Secondary outcomes were disease free survival (DFS) and overall survival (OS). Materials and Methods: This non-randomize prospective phase II stud was performed at Jordan University of Science and Technology and its affiliated King Abdulla Teaching Hospital between July 2009 and August 2010. Data collection was closed on May 31th, 2015 giving a median follow up period of 62 months. The study was approved by the institutional review board and a written informed consent was obtained for each patient. Results: Fifty patients were enrolled. The median age was 53.1 years (range 34-76). One patient (2%) had stage I disease, 17 (34%) stage II, and 32 (64.0%) stage III. Forty-six patients were evaluable for efficacy analysis. The completion rate was 95.7%. No dose modifications were needed. The incidences of grade 3-4 neutropenia and febrile neutropenia were 14 % and 10%. No grade 3-4 non-hematological adverse events were encountered. At a median follow up time of 62 months the OS and the DFS rates were 76.1% and 56.5%. Those for stages I and II combined were 100% and 75%. Conclusions: Taxotere first followed by doxorubicin-cyclophosphamide appears a feasible regimen as evidenced by an acceptable completion rate, a satisfactory safety profile, and an OS and DFS rates comparable to other studies.

Keywords: Adjuvant chemotherapy - breast cancer - anthracycline - sequential docetaxel

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Introduction

Anthracycline based regimens are highly effective in the adjuvant treatment of breast cancer. In a meta-analysis of randomized trials, six cycles of anthracycline-based chemotherapy were associated with an annual reduction of breast cancer death rate by 38% for women younger than 50 years of age, and by 20% for those aged 50-69 years (Early Breast Cancer Trialists' Collaborative Group, 2005). However, the applicability was hampered by the toxicity profile including cardiac toxicity. Ongoing trials were exploring other drugs with same efficacy, yet avoiding the cardiac toxicity nightmare. In this context, and based on a significant activity in the metastatic setting, taxanes have been extensively evaluated in the adjuvant setting (Roché et al., 2006; Francis et al., 2008). A meta-analysis of 13 randomized studies including 22,903 patients demonstrated that the addition of a taxane to an anthracycline based regimen was associated with an improved disease free survival (DFS) and overall survival (OS) (De Laurentiis et al., 2008). So, anthracycline and taxane based regimens are now considered the most active agents in the adjuvant treatment (Denduluri et al., 2016). They can be used concomitantly or sequentially. The best order in the sequential regimens is not yet determined, but most patients will traditionally receive the anthracyclines first. Interestingly, there was evidence that the sequential docetaxel first followed by anthracycline regimen was associated with an improved DFS, and similar OS (Polyzos et al., 2010). Two other reports pointed toward an improved patient compliance when applying the taxanes first (Piedbois et al., 2007; Puhalla et al., 2008).

Patient compliance to receive the full number of cycles per protocol will logically be associated with a better outcome, yet the effect on patient's quality of life should be minimal. At our center only 70 % of patients manage to receive 4 cycles of Taxotere (T) after previous 4 cycles of doxorubicin-cyclophosphamide (AC). This might be a result of toxicity related factors, but it might be partly related to the fact that they have become less tolerant due

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to the previous experience with AC. To address this, we have designed this study to evaluate the feasibility of 4 cycles of T to be followed by 4cycles of AC in the adjuvant treatment of breast cancer.

The primary objective was the Safety Profile (SP). Secondary objectives were the DFS and the OS.

Materials and Methods

This is a non-randomized, prospective, single-arm, phase II study to assess the feasibility of 4 cycles of T followed by 4 cycles of AC in the adjuvant treatment of operable breast cancer patients. The study will be performed at the Faculty of Medicine at Jordan University of Science and Technology, and affiliated King Abdulla Teaching Hospital, between July 2009-August 2010. For the purpose of writing this report, data were closed on May 31th, 2015 getting a median follow up period of 62 months (10-74).

Inclusion and exclusion criteria

Female patients aged 18 years and above, with histologically proven diagnosis of stage I, II, or III invasive breast carcinoma considered suitable for adjuvant treatment, will be allowed for enrollment. Initial surgical treatment is by mastectomy (or conservation breast surgery) and axillary lymph node dissection. Radiotherapy is mandatory in patients undergoing conservation surgery. Patients should have an adequate bone marrow, hepatic, and renal functions as evident by: Hemoglobin ≥ 10 g/d L, absolute neutrophils count ≥ 2000/mm^2, platelets count ≥ 100000/mm^2, total bilirubin ≤ 1× Upper Normal Limit (UNL), SGOT (AST), SGPT (ALT) and alkaline phosphatase ≤ 2.5 UNL, creatinine ≤ 1.5 UNL. WHO performance status should be ≤2. Patients should have no psychological, familial, or sociological, conditions potentially hampering compliance with the study protocol. Pregnancy, lactation, current peripheral neuropathy ≥ grade (G) 2 according to National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Version 3.0. , history of other malignancy within the past five years, and severe impaired renal function (creatinine clearance less than 30 ml/min) will exclude recruitment.

The study has been approved by the institutional review board (IRB). A written informed consent was obtained for each patient.

Staging work up included a bone scan, and a CT scan of chest and abdomen. Adequate blood counts and liver and kidney function tests were assured before each cycle as evident by: Hemoglobin ≥ 10 g/d L, absolute neutrophils count ≥ 2000/mm^2, platelets count ≥ 100000/mm^{2,} total bilirubin ≤ 1× Upper Normal Limit (UNL), SGOT (AST), SGPT (ALT) and alkaline phosphatase ≤ 2.5 UNL, creatinine ≤ 1.5 UNL.

No primary or secondary prophylaxis by granulocyte colony stimulating factor (G-CSF) was used.

The regimen will be considered feasible if the patient receives at least 7-cycles with a satisfactory clinical evaluation, as judged by the treating physician after each cycle, including the hematological and the non-hematological adverse events (AE). All the 'intend to treat population' will be evaluated for SP. Evaluable patients for efficacy are those who finish at least 7 cycles, or those receiving less than 7 cycles as a result of AE, patient intolerability, disease progression, or death during treatment.

A follow up bone scan, and CT abdomen and chest were performed after full recovery from the last cycle. Further work up was guided by the clinical situation. For the purpose of writing this report, data were closed on May 31th, 2015 getting a median follow up period of 62 months.

Adjuvant trastuzumab was given for one year for patients over-expressing human epidermal growth factor 2 (HER 2). Adjuvant anti-estrogen treatment for estrogen receptor positive patients consisted of tamoxifen for premenopausal patients and tamoxifen or specific aromatase inhibitors for postmenopausal patients.

AE were graded according to NCI CTCAE Version 3.0.

Statistics

Descriptive analysis using SPSS Statistics 17.0 was used.

OS and DFS were estimated using the Kaplan-Meier method.

Assuming an expected response of P= 75%, based on the reported literature (Piedbois et al., 2007; Puhalla et al., 2008), and that the standard deviation is 15% from P, and applying the formula : (Standard Deviation)2 =4PQ/N where Q=1-P and N is the size of the sample, 50 patients were needed.

The percentage of patients receiving at least 7 cycles of chemotherapy in the AC followed by T regimen at our center ranged from 65-75 %. So, in order for the T followed by AC regimen to be considered feasible and clinically justified, at least 75% of the patients should receive a minimum number of 7 cycles.

Hundred percent of the first 16 enrolled patients received at least 7 cycles of chemotherapy, and in view of this, further enrollment was clearly justified.

Treatment details

4 cycles of T every 3 weeks to be followed by 4 cycles of AC every 3weeks.

Doses: T 100mg/m^2 by 60 min intravenous infusion. Premedication consisted of oral dexamethasone 8 mg twice a day for three days starting the morning prior to chemotherapy. The starting dose of the first cycle of T was 75mg/m2. Subsequent cycles were continued at the 100mg/m2 dose thereafter.

A: 60 mg/m^2 C: 600mg/m^2

Results

Between July 2009-August 2010, 50 patients were enrolled. Table 1 summarizes the general patient characteristics. The median age was 53.1 years. One patient (2 %) had stage I disease. Seventeen patients (34%) had stage II, and 32 patients (64%) had stage III disease. The median tumor size was 4 cm (range 1-17). The median number of involved lymph nodes was 4

(range 0-36). The median follow up time was 62 months (10-74). WHO performance status was 0 in 30 patients, 1 in 15 patients, and 2 in 5 patients. All enrolled patients (50 patients) were evaluated for SP. Four patients were considered non-evaluable for efficacy, leaving 46 patients for efficacy analysis. The reasons for this were: One patient from a nearby country received the first cycle of T and elected to continue treatment outside. One patient received 4 cycles of T and decided not to receive AC: this was not due to side effects of T, but the patient was too much worried about A related cardiomyopathy. Two patients decided to go back to AC cycles after receiving the first cycle of T and changed their consent. This was not due to intolerability of the first dose of T, but the patient's decision. The number of patients receiving at least 7 cycles of chemotherapy was 44. (95.7%) The number of patients receiving 8 cycles of chemotherapy was 40. (87%) Two patients (4.3%) received 6 cycles of chemotherapy: In one patient, this was due to two consecutive attacks of G3 neutropenia (N) in the first and second cycles of T. No further cycles of T were given .The patient received further 4 cycles of AC. The second patient received 4 cycles of T and two cycles of AC and she refused further cycles of chemotherapy due to non-specific subjective intolerability. The number of patients tolerating 4 cycles of T was 45. (97.8%) No dose modifications were needed. This remarkably excellent compliance was also noticed in the number of patients completing their planned 4 cycles of AC. (41 Patients, 89.1%) Four patients received 3 cycles of AC. (8.7%) One patient received 2 cycles of AC. (2.2%) The median number of chemotherapy period received was 168 days. (Range168-178)

Table 1. General Characteristics of 50 Patients Receiving Adjuvant Taxotere Followed by Adriamycin-Cyclophosphamide

Age of Pateints	Median 53.1 (34 Yrs. – 76 Yrs.)		
Marital status	Single		1 (2%)
	Married		49 (98%)
Type of surgery	Modified radical mastectomy with axillary clearance		50 (100%)
	Wide local excision with axillary clearance		0 (0%)
Histological types	Invasive ductal		47 (94%)
	Invasive lobular		3 (6%)
Stage at diagnosis	Stage I		1 (2%)
	Stage II		17 (34%)
	Stage III		32 (64%)
	Stage IV		0 (0%)
TNM classification	T	Tx	1 (2%)
		T1	6 (12%)
		T2	26 (52%)
		T3	17 (34%)
		T4	0 (0%)
	N	Nx	2 (4%)
		N0	4 (8%)
		N1	14 (28%)
		N2	15 (30%)
		N3	15 (30%)
	M	M0	50 (100%)
		M1	0 (0%)
Tumor receptor status	Estrogen	Positive	30 (60%)
		Negative	20 (40%)
	Progesterone	Positive	29 (58%)
		Negative	21 (42%)
	HER-2-neu	Positive	16 (32%)
		Negative	26 (52%)
		Equivocal	8 (16%)
Radiotherapy		Received	28 (56%)
		Not received	22 (44%)
Trastuzumab		Received	11 (22%)
		Not received	39 (78%)

Primary end point

Hematological AE: The hematological AEs are summarized in Table 2. The incidence of G3-4 N and febrile neutropenia (FN) were 14% and 10 %. Among evaluable population, only one patient received less than the 4 scheduled cycles of T (2 cycles) because of two consecutive attacks of G3 N in the first cycle (day 9) and the second cycle (day 7). She presented on day 9 of the first cycle, with G2 fatigue, and was found to have G3 N. She was given G-CSF and responded promptly. The second cycle was given with no delay. On day seven of the second cycle she was found to have G3 N. She was given G-CSF. The treating physician decided not to give further T, and treatment was continued using AC.

In general, no dose reductions were needed in the subsequent cycles after N or FN occurring in a previous cycle. The reasons for cycle delay were hematological (N). No delay was related to non-hematological AE. The number of patients in whom the cycle was delayed was 6 patients (16 %) with an average delay of 4.2 days.

The incidence of G 3 -4 anemia among our patients was 4%.

Non-hematological AE

Table 3 lists the non-hematological AEs. No G3 or G4 AEs were observed. No serious AEs were encountered. No patient died as a result of treatment related toxicity. No patient died during the treatment study period.

Secondary end points

The OS curve is demonstrated in Figure 1. At a median follow up time of 62 months the OS rate was 76.1%. The DFS is demonstrated in Figure 2. At a median follow up

Table 2. Hematological adverse Events Observed among 50 Patients Receiving Adjuvant Taxotere Followed by Adriamycin-Cyclophosphamide

	None		Grade1		Grade2		Grade3		Grade4		Grade5		Total	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Febrile neutropenia	-		-		-		5	10	0	0	0	0	5	10
Neutropenia	37	74	1	2	5	10	4	8	3	6	0	0	13	26
Thrombocytopenia	49	98	0	0	1	2	0	0	0	0	0	0	1	2
Anemia	46	92	0	0	5	10	1	2	1	2	0	0	7	14

Table 3. Non-Hematological Adverse Events Observed among 50 Patients Receiving Adjuvant Taxotere Followed by Adriamycin-Cyclophosphamide

	Grade1		Grade2		Grade3		Grade4		Grade5	
	NO.	%	NO.	%	NO.	%	NO.	%	NO.	%
Alopecia	0	0	49	98	-		-		-	
Diarrhea	0	0	2	4	0	0	0	0	0	0
Dyspepsia	5	10	0	0	0	0	-		-	
Gastritis	0	0	5	10	0	0	0	0	0	0
Esophagitis	0	0	2	4	0	0	-		-	
Muositis, Oral cavity	0	0	3	6	0	0	0	0	0	0
Nausea	11	22	11	22	0	0	-		-	
Vomiting	12	24	10	20	0	0	0	0	0	0
Dysguisia	2	4	0	0	-		-		-	
Fatigue	8	16	5	10	0	0	-		-	
Allergic reaction	2	4	1	2	0	0	0	0	0	0
Infusion site reaction (extravasation)	0	0	2	4	0	0	0	0	0	0
Pain – joint (Arthralgia)	11	22	8	16	0	0	-		-	
Neuropathy- Sensory	4	8	2	4	0	0	0	0	0	0
Nail changes	10	20	4	8	-		-		-	
Skin hyperpigmentation	5	10	0	0	-		-		-	
Urticaria	1	2	2	4	0	0	-		-	

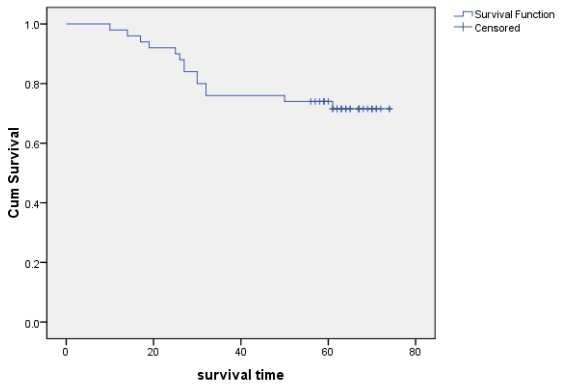

Figure 1. Overall Survival Curve among Patients Receiving Taxotere Followed by Adriamycin-Cyclophosphamide for Early Breast Cancer

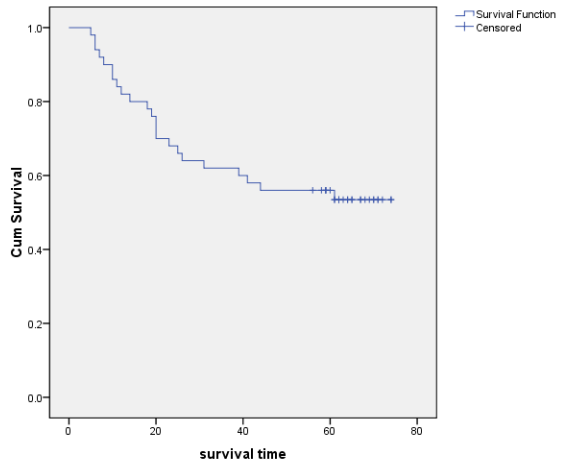

Figure 2. Disease Free Survival Curve among Patients Receiving Taxotere Followed by Adriamycin-Cyclophosphamide for Early Breast Cancer

time of 62 months, the DFS rate was 56.5%. The OS and the DFS rates among stage I and Stage II patients were 100% and 75 %.

Discussion

In order to interpret the data in this report, few basic epidemiological points regarding breast cancer in Jordan are worth mentioning. About 37% of Jordanian people are below the age of 15 years leading to a younger median age at presentation compared to western countries (Al-Muqbel and Yaghan, 2013). Breast cancer in the young tends to be associated with a more advanced stage at presentation (Al-Muqbel and Yaghan, 2013). On the other hand, the prevalence of co-morbid conditions is expected to be lower. Younger patients are expected to tolerate chemotherapy with relatively fewer AE (Reinisch et al., 2013). In this study group, 2 % of the patients presented with stage I disease, and 64% presented with stage III.

The completion rate of (4T followed by 4 AC) was 95.7%. This tendency toward an improved compliance rate when applying the taxane first in sequential regimens was also noticed in other reports (Thiery-Vuillemin et al., 2011; Abe et al., 2013) Two other randomized phase II studies with dose -dense adjuvant chemotherapy highlighted the interest of administering taxane before anthracycline (Piedbois et al., 2007; Puhalla et al., 2008). They were associated with fewer docetaxel dose reductions and higher dose intensity than the reverse sequence. Another retrospective study, in the neoadjuvant setting, demonstrated that the overall dose intensity of docetaxel was higher when docetaxel was given before the anthracycline containing regimen (Thiery-Vuillemin et al., 2011). Better compliance will logically lead to a better outcome.

In our study, the rate of G3-4 N and FN were 14%, and 10%. The younger age at presentation, alluded to above, might have contributed partially to this relatively low rate of N (Reinisch et al., 2013). It is worth mentioning here that the incidence of N in this study was calculated depending on systematic hematological tests done before each cycle unless there was a clinical reason to do the testing in between the cycles. This will lead to under-

diagnosis of N but reflects at the same time the real clinical practice. In keeping with our results, another study reported a tendency toward a reduced myelosuppression when applying the adjuvant taxane first (Abe et al., 2013). Two randomized phase II studies with dose -dense adjuvant chemotherapy showed less G3-4 N and FN in the arms applying docetaxel before anthracycline (Piedbois et al., 2007; Puhalla et al., 2008). In contrast to our results, another study reported a 7.7% rate of FN and a 72.2% rate of N (Polyzos et al., 2010).

Interestingly, starting chemotherapy by taxane was reported to be associated with a reduced occurrence of anemia, allowing a selection of the sequence order based on the toxicity profile (Thiery-Vuillemin et al., 2011). The incidence of G 3-4 anemia among our patients was 4%.

Among our study group, the non-hematological AE were tolerable and no patient stopped treatment as a result of this. Particularly, the rate and G of nausea and vomiting were equal, or less than, reported in other studies implementing sequential regimens (Abe et al., 2013; Kim et al., 2016). Lower incidence of nausea and vomiting, might be associated with a better psychological impact on patients, facilitating the acceptance of the initial phases of treatment (Thiery-Vuillemin et al., 2011).

The OS and DFS rates among stage I and Stage II patients were 100% and 75 %, which is comparable to other reports (Piedbois et al., 2007; Puhalla et al., 2008). The OS rate was 76.1% and the DFS rate was 56.5 % for stages I,II, and III. Taking into consideration that 64% of our patients were having stage III disease and only 2% of them had stage I, these figures are quite satisfactory and comparable to other data (Polyzos et al., 2010). In keeping with this, in a randomized multicenter phase III study comparing the treatment outcome of 4 cycles of T followed by 4 cycles of epirubicin (E)-C compared to 6 cycles of 5-flourouracil-E-C, the sequential docetaxel first followed by anthracycline regimens was associated with an improved five-year DFS, and a similar OS (Polyzos et al., 2010). An improved outcome was also noticed in the neoadjuvant and metastatic settings when applying docetaxel first. The clinical complete responses were significantly higher when neoadjuvant docetaxel was given before the anthracycline (Thiery-Vuillemin et al., 2011). A higher response rate for metastatic breast carcinoma was reported when docetaxel was given before EC (Spielmann et al., 2002).

In conclusion, the sequential (T followed by AC) regimen was feasible as evident by a satisfactory SP and a high completion rate. The OS and DFS were comparable to other studies.

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