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Feasibility of Concurrent Radiotherapy and Paclitaxel-Based Chemotherapy after Conservative Surgery for Breast Cancer

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Abstract

Purpose: Our prospective phase II trial aims to show the feasibility of adjuvant paclitaxel-based concurrent chemoradiotherapy (CCRT) following doxorubicin and cyclophosphamide (AC) to get the survival benefit of taxanes addition and avoid delay of radiotherapy. **Patients and Methods:** A total of 63 patients with pT1-2, and pN1-3, M0 breast cancer underwent conservative surgery followed by adjuvant 4 cycles AC followed by 4 cycles Paclitaxel 175 mg/m^2 every 3 weeks. Adjuvant radiotherapy started during the first and second cycle of paclitaxel (CCRT). Toxicities evaluated at the base time, weekly during radiation therapy and every 3 months for 24 months for skin, pulmonary, cardiac, lymphedema, subcutaneous fibrosis and cosmoses. Survival reported at 2-year median follow-up. **Results:** At median follow up time of 24 months (6 - 30), we did not report any toxicity postpone or stop treatment and only two patients had grade III acute dermatitis. Fifty-two patients (82.5%) had satisfactory cosmoses and none of the patients developed local recurrence. **Conclusion:** Three-weekly paclitaxel during radiotherapy is considered safe without significant complications and acceptable cosmoses with excellent local control and could be considered to avoid radiotherapy delay.

Keywords

Breast Cancer, BCS, Concurrent Radiotherapy and Paclitaxel

1. Introduction

Most of the studies could not reveal a significant difference between different radiotherapy and chemotherapy sequences in breast cancer adjuvant sitting [1]. Radiotherapy is used in general after completion of adjuvant chemotherapy that could adversely affect locoregional control [2].

Concurrent radiotherapy and chemotherapy is an attractive choice completely removes this conflict. Furthermore, cyclophosphamide, methotrexate and 5-fluorouracil (CMF) regimen concurrently with radiotherapy have been proved to be safe [3] and showed an increased locoregional control without additional toxicities compared to sequential protocols [4]. However, most adjuvant regimens nowadays use anthracycline and taxane-based regimens as it increased survival [5].

Paclitaxel has *in vitro* radio-sensitization for many human tumour cell lines including breast cell line (MCF-7), and it acts as a microtubule-stabilizing agent and promoter of microtubule assembly, blocking or prolonging the transit time of cells in a more radiosensitive G2/M cell cycle phase [6]. It is a well-known radiosensitizer that could increase locoregional control; on the other hand, it could increase toxicities [7].

2. Patients and Methods

Our study was conducted prospectively and approved by our institutional review board with informed written and oral consents being obtained from all participating patients. The study included 63 female patients diagnosed with breast cancer in the period from May 2014 to November 2016. The patients were referred from the outpatient clinic of South Egypt Cancer Institute, Assiut University. Eligibility criteria included invasive adenocarcinoma of the breast; pT1-2, and pN1-3, M0, Age ≥ 18 and ≤70; PS ≤ 2 (ECOG), underwent BCS with histologically negative margins and normal hematopoietic, hepatic, and renal function tests as well as cardiac functions. Patients were given trastuzumab and hormonal therapy when indicated. Currently, pregnant patients and patients with the previous history of malignancy or radiotherapy as well as connective tissue or neuropathic diseases were excluded from the study.

1) Treatment:

Patients were evaluated clinically before treatment followed by echocardiographic examination for detailed assessment of the performance status, left ventricular ejection fraction (LVEF), chest CT, pulmonary function tests (PFT) and complete laboratory investigations.

a) Surgery:

All patients underwent Breast conservative surgery where lumpectomy was done in 25 patients, wide local excision (20 patients), quadrantectomy (10 patients), and segmental resection in 8 patients.

Skin incisions are done through a circumareolar incision in centrally located lesions and through natural lines of the breast in other sites to optimize cos-

moses.

b) Chemotherapy:

Following breast conservative surgery (BCS), all patients received 4 cycles of chemotherapy in the form of doxorubicin and cyclophosphamide (AC) (60 mg/m^2 and 600 mg/m^2 respectively), followed by four cycles of paclitaxel (175 mg/m^2), the cycles were given every three weeks.

c) Radiotherapy:

Radiotherapy started concurrently with the first and second cycles of paclitaxel. Chemo-radiation therapy was stopped in case of GIII dermatitis, GIII pneumonitis, >10% decrease EF or severe hematologic toxicities.

Breast target volume as identified on CT with previous breast demarcation, excluding 0.5 cm skin thickness. Tumor bed was delineated using clinical data before surgery, lumpectomy cavity seroma or surgical clips, and scar. Supra-clavicular and infra-clavicular lymph nodes were irradiated per Radiation Therapy Oncology Group (RTOG) atlas contouring [8] and axillary irradiation was done in case of incomplete evacuation, however, internal mammary nodes were not irradiated unless radiologically enlarged.

The total dose for breast and nodal irradiation was 5000 cGy in 25 fractions in 5 weeks and the tumour bed received boost dose of 14 Gy in 7 fractions in patients younger than 50 years.

We carried out 3D plan using wedges and field in the field, according to ICRU 50 constraints [9].

2) Assessment:

Patients were examined before radiotherapy, weekly during treatment, every three months for 2 years and every 6 months thereafter. They were evaluated for tumour recurrence, different toxicities (skin, subcutaneous tissue, cardiac, pulmonary, lymphedema or brachial plexus injury). The relevant required investigation was done accordingly.

Acute skin toxicities were assessed weekly during radiation and at 1.5 months after completion of treatment based on the criteria of RTOG [10]. Late skin toxicities (telangiectasia, hyperpigmentation, atrophy, erythema, skin oedema, dimpling or indentation) and subcutaneous fibrosis were assessed every 6 months using the modified late effects on normal tissue scoring system [11].

Radiation pneumonitis symptoms were evaluated at 3 weeks, 3 months, 6 months and 12 months after radiotherapy according to RTOG scoring criteria [10]. PFT including forced vital capacity (FVC) and forced expiratory volume in one second (FEV1) were evaluated by the dry sealed sensor medics computerized spirometer (SER 54065; sensor medics corporation, USA). The grading of PFT (per NCI/SWOG) was done according to the decrease in measurements compared to pretreatment value and classified into GI, II, and III for reduction to ≥90%, ≥75% - <90% and ≥50% - <75% of pretreatment value respectively [12]. Computerized tomography (CT) of the chest was done prior to treatment as a baseline investigation, then at 3 and 9 months after radiotherapy comple-

tion. Pulmonary changes were scored according to Nashik scoring system [13] based on significant radiological changes within the radiation field (Grade 0, no changes; Grade 1, only pleural thickening; Grade 2, plaque-like or heterogeneous density in <50% area of radiation fields; and Grade 3, pulmonary changes in >50% area of radiation fields).

Cosmoses were assessed by Harvard scale [14], where the treated breast was compared either to the untreated breast or to the original appearance of the treated breast. The recorded differences in size, shape or texture were graded as excellent, good, fair, and poor.

The arm circumference was measured on both sides at 10 cm above and below the olecranon process of ulna just before radiotherapy treatment and at 3, 12 and 24 months following radiotherapy treatment to assess lymphedema, which was graded as I, II, and III upon circumference increase of 0 - 1 cm, 1 - 2 cm and >2 cm respectively [12]. Magnetic resonance imaging (MRI) examination was performed in case of suspicion of brachial plexus injury.

Statistical Analysis

Data represented as frequencies and percentages. Univariate factors were analyzed using the chi-square test for categorical variables. DFS calculated from the first date of treatment by the Kaplan-Meier method. $P \leq 0.05$ was considered significant. Data were analyzed using SPSS version 20.

3. Results

This study included 63 patients with node-positive operable breast cancer who underwent BCS and received adjuvant 4 cycles of AC followed by 4 cycles of paclitaxel, the first 2 cycles of paclitaxel administered concurrently with radiotherapy. Patients' characteristics and demographics are summarized in **Table 1**.

1) Toxicities

a) Skin toxicities:

Grade II acute skin reaction was detected in 19 patients (30.1%) and two patients (3.2%) had grade III toxicities that occurred at last day of booster dose (**Table 2**). None of them required treatment interruption or therapy break and all of them showed regressive course of the reaction with complete resolution 6 weeks after treatment.

Chronic skin toxicity was detected in 2 patients (3.2%) with grade I chronic radiation dermatitis and 1 patient (1.6%) with grade II late skin reaction (**Table 3**). None of the patients had grade III telangiectasia, and hyperpigmentation reported as grade I in two patients and grade II in one patients that subsided grade I at 2 years.

b) Subcutaneous fibrosis:

Grade I subcutaneous fibrosis was detected in 9 patients (14.3%) and grade II in 3 patients (4.8%) (**Table 4**).

c) Pulmonary toxicities:

Table 1. Patients' and tumor characteristics of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Variable	Number	%
Age (years)		
<50	35	55.6
≥50	28	44.4
Median	47	
Range	25 - 69	
Menopausal status		
Premenopausal	48	76.2
Postmenopausal	15	23.8
Laterality		
Left	34	54.0
Right	29	46.0
Site		
Upper outer	32	50.8
Upper inner	9	14.3
Lower outer	12	19.0
Lower inner	8	12.7
Central	2	3.2
T Stage		
pT1	17	27.0
pT2	46	73.0
Nodal stage		
pN1	34	54.0
pN2	25	39.7
pN3	4	6.4
Histology		
Ductal	58	92.1
Lobular	5	7.9
Grade		
Well	12	19
Moderate	50	79.4
Poor	1	1.6
ECE		
No	54	85.7
Yes	9	14.3
LVI		
No	50	79.4
Yes	13	20.6
Hormone receptor		
Positive	34	54.0
Negative	20	31.7
Unknown	9	14.0
HER2 status		
Negative	43	68.3
Positive	11	17.5
Unknown	9	14.3
Hormonal therapy		
Tamoxifen	10	15.9
Aromatase Inhibitors	33	52.4
No	20	31.7

Table 2. Acute radiation dermatitis of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Grade	Number	%
GI	42	66.7
GII	19	30.1
GIII	2	3.2

Table 3. Chronic radiation dermatitis of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Grade	Number	%
G0	60	95.2
GI	2	3.2
GII	1	1.6

Table 4. Subcutaneous fibrosis of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Grade	Number	%
G0	51	81.0
GI	9	14.3
GII	3	4.8

Acute radiation pneumonitis was observed in 11 patients (17.5%), 3 of them were grade II with no need for steroids (Table 5). The time range from the end of radiotherapy till the appearance of acute radiation pneumonitis was 4 - 12 weeks (mean 6 weeks). Five patients showed chronic pulmonary pneumonitis; 4 (6.3%) were grade I and one patient (1.6%) was grade II (Table 6). PFT changes revealed grade I toxicity only, but no grade II toxicity. They were detected in 23 patients (36.5%) and 4 patients (6.3%) at 3 and 24 months respectively.

Assessment of CT pulmonary changes at 3 months revealed grade I, II and III changes in 3.2%, 3.2% and 1.6% of the patients respectively that showed regression or resolution to 3.2%, 1.6% and 0% respectively (Table 7).

Patient and tumour parameters (age, menopausal status, laterality, site, T stage, N stage, histology, grade, ECE, LVI, Hormone receptor status, HER2 status, hormonal therapy and median separation of the tangent at central axis) were not significant factors for the occurrence of radiation-induced pneumonitis.

d) Cardiac toxicities:

One patient only showed 10% decrease of LVEF without any notable cardiac symptoms.

e) Cosmoses:

Fifty-two patients (82.5%) showed acceptable outcome (Table 8).

f) Lymphedema:

Three patients (4.8%) showed grade II lymphedema.

g) Brachial plexus injury:

Table 5. Acute pulmonary toxicities of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Grade	Number	%
G0	52	82.5
GI	8	12.7
GII	3	4.8

Table 6. Chronic pulmonary toxicities of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Grade	Number	%
G0	58	92.1
GI	4	6.3
GII	1	1.6

Table 7. Post-radiation CT lung changes of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Grades	Baseline No (%)	3 months No (%)	9 months No (%)
G0	63 (100)	58 (92.1)	60 (95.2)
G1	0	2 (3.2)	2 (3.2)
G2	0	2 (3.2)	1 (1.6)
G3	0	1 (1.6)	0

Table 8. Cosmetic outcomes using Harvard Scale of patients undergoing adjuvant concurrent chemoradiotherapy for breast cancer (n = 63).

Variable	Number	%
Excellent	19	30.2
Good	33	52.4
Fair	8	12.7
Poor	3	4.8

None of the patients showed symptoms suggesting brachial plexus injury.

2) The pattern of failure of treatment:

After a median follow-up time of 24 months (range, 6 - 30 months), two patients (3.2%) developed distant metastasis (bone after 15 months and lung after 18 months), but no patients showed local failure. The 2-year disease-free survival (DFS) rate was 96.6%, (Figure 1). None of the prognostic factors (age, menopausal status, laterality, site T state, N stage, TNM stage, histology, grade, ECE, LVI, Hormone receptor status, HER2 status and hormonal therapy) showed significance for DFS.

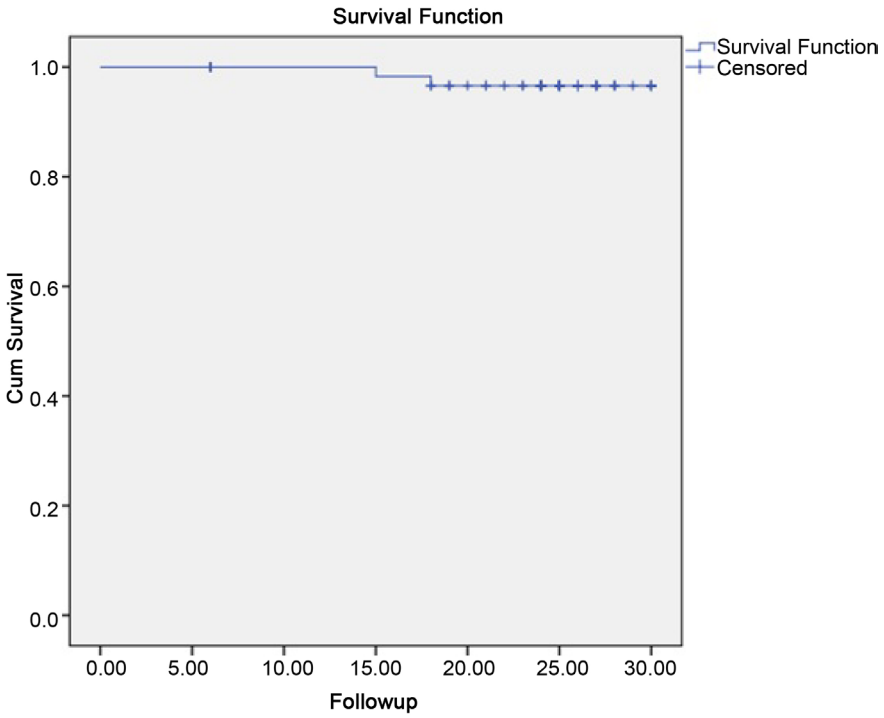

Figure 1. Showed the 2-year disease free survival rate in 63 patients with node positive breast cancer.

4. Discussion

Adjuvant chemotherapy and radiotherapy have established roles in breast cancer treatment. Addition of taxanes to ananthracycline-based chemotherapy regimen in adjuvant setting has shown improvement of survival [5], however, this prolonged chemotherapy course and delayed radiation could affect local control of the disease and DFS [15]. Until now, there is no ideal radiotherapy and chemotherapy sequence [1].

The application of concurrent chemoradiotherapy has shown both efficiency and tolerability in different cancers as cervix, oesophagus, lung and rectum. However, its role as an adjuvant treatment in breast cancer is still under debate [16] [17] [18].

Aiming for toxicity reduction, paclitaxel every 3 weeks concurrently with adjuvant breast radiotherapy was used instead of weekly paclitaxel [19] [20]. Radiotherapy was not started during anthracycline-based chemotherapy to avoid severe skin toxicity [21]. We did not include mastectomized patients as different cosmetic results and more radiation toxicities as we consider chest wall irradiation [19].

Our study showed no severe toxicity that caused interruption of treatment with paclitaxel (175 mg/m^2/3weeks) based concurrent chemoradiotherapy (50 Gy).

All acute and chronic skin toxicities were mild with only two patients showed grade III toxicity at the end of radiotherapy at boost areas, which showed rapid

resolution without interference. Such a finding may confirm the dermatological safety of our protocol, which is in accord with previous studies [22]. However, the final results of the ARCOSEIN trial [16] showed more skin toxicity, which may be attributed to the combined use of both doxorubicin and cyclophosphamide concurrently with radiotherapy.

We used Harvard scale [14] to evaluate cosmetic outcome after breast conservative surgery (BCS). Despite its rapid and easy application, operator dependency is considered its major disadvantage [23], which was overcome in our study by recruiting experienced doctors for assessment and analysis. The majority of our patients (82.5%) showed satisfactory objective and subjective response with only 4.8% showed poor cosmetic outcome, which is concordant with the results of Chen *et al.* [22].

Paclitaxel is known of its pulmonary toxicity [24], therefore, radiation pneumonitis was evaluated by clinical examination, CT chest examination and PFT. Our results showed only mild respiratory symptoms and no severe toxicity that did not deserve interruption of treatment or steroid administration. Higher rates of radiation pneumonitis were detected upon using weekly paclitaxel concurrently with adjuvant breast radiotherapy [24], upon including chest wall in radiation clinical target volume [19], or using methotrexate containing regimen (CMF), which may potentiate lung fibrosis [25].

There is no serious cardiac complications or increased incidence of lymphedema, which may be attributed to the application of CT based target delineation of supraclavicular and infraclavicular lymph nodes without axillary irradiation and with relative small clinical target volume (CTV) for nodal irradiation to ensure radiation coverage [22] and avoid unnecessary soft tissue irradiation outside target nodal areas.

Our protocol achieved comparable short-term survival data [26] with excellent local control as we reported 96% 2-year DFS and none of the patients developed local recurrence, however longer follow up on a larger number of patients is recommended to document the expected survival benefits of concurrent chemoradiotherapy in the adjuvant setting for breast cancer.

5. Conclusion

Our findings of this prospective Phase II trial support the safety of paclitaxel every 3 weeks given concurrently during radiotherapy in the adjuvant setting after breast-conserving surgery with excellent local control, acceptable tolerability, pulmonary and skin complications in addition to acceptable cosmoses without delay of radiation. However, further studies on a larger scale of patients with longer follow up using concurrent paclitaxel with the new standard breast hypofractionated radiotherapy may be useful and recommended.

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