Comparative Study of the Combination of Trastuzumab with Conventional Radiotherapy versus Trastuzumab with Hypofractionated Radiotherapy in HER2/neu Positive Breast Cancer

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Abstract:

Background: Despite the frequent combination of trastuzumab and irradiation in breast cancer treatment, there is little evidence about the safety of their concurrent adjuvant administration, particularly with hypo fractionated radiation therapy (Hypo-RT). We conducted this study to examine the safety of concurrent administration of Trastuzumab with conventional radiation (Conv-RT) compared to Trastuzumab with Hypo-RT in Her2/neu breast cancer, focusing on cardiac and cutaneous toxicities.

Methodology: This prospective randomized open-label study included 150 patients with localized breast cancer who were referred to the medical and radiation oncology departments at South Egypt Cancer Institute, Assiut University, from July 2018 to January 2024. Arm A (Conv-RT) included 100 patients, whereas arm B (Hypo-RT) had 50 patients.

Results: There is no significant difference in the reduction of LVEF from baseline between the groups (p=0.080), with the majority of patients in both groups showing a reduction of less than 10%. Cardiac toxicity, whether asymptomatic or symptomatic, is also comparable between the two groups (p=0.203). Furthermore, all non-cardiac toxicities were acute and only grade I-II with the exception of lymphedema. There was lower incidence acute skin toxicity (10% versus 27%), fatigue (2% versus 7%), breast pain (4% versus 10%) with equal percentage of lymphedema cases (2%) in Hypo-RT compared with conventional RT, respectively.

Conclusion: Hypo-RT administered concurrently with trastuzumab is safe and feasible with lower incidence of cardiac and skin toxicities compared with conventional RT in adjuvant breast cancer patients.so, longer follow-up period is needed to determine long term results.

Keywords: Breast cancer, HER2/neu positive, Trastuzumab, hypofractionated radiotherapy, conventional radiotherapy

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Introduction:

Breast cancer is the most common disease among women in the United States, accounting for 32% (310,720 cases) of all newly diagnosed cancer cases and the second largest cause of cancer mortality, representing 15% (42,250 cases) of all cancer deaths in 2024. Approximately 91% of patients had locoregional illness, with 25% demonstrating nodal positive. [1]. In Egypt, the estimated breast cancer incidence rates among females were 33.2% in Lower Egypt from 2009 to 2011, 26.8% in Middle Egypt in 2009, and 38.7% in Upper Egypt in 2008. An extensive Egyptian institutional epidemiological research including 1906 breast cancer patients treated over five years revealed that 74% were diagnosed with locoregional disease, of whom 57% had node-positive disease [2, 3].

The HER2 gene is overexpressed in around 20% of breast cancer patients, which is associated with a worse prognosis and more aggressive disease activity [4, 5]. Trastuzumab, the first humanized monoclonal antibody targeting HER2, was approved by the FDA in 2006 for adjuvant treatment in HER2-positive breast cancer, based on extensive trials demonstrating enhanced

overall survival and decreased recurrence rates [6, 7]. Trastuzumab therapy is often well-tolerated; nonetheless, its cardiotoxicity, which varies from asymptomatic reductions in LVEF to symptomatic heart failure, remains a significant issue [8].

Postoperative radiation therapy to the breast after breast-conserving surgery or mastectomy enhances locoregional control and long-term survival rates [9]. Conventional radiotherapy has been the usual treatment; however, current worldwide guidelines now advocate for hypofractionated irradiation for patient convenience [10].

Despite the frequent combination of trastuzumab and irradiation in breast cancer treatment, there is little evidence about the safety of their concurrent adjuvant administration, particularly with hypofractionated radiation therapy. This research assesses the safety of concurrent administration of Trastuzumab with conventional radiation compared to Trastuzumab with Hypo-RT in Her2/neu breast cancer, focusing primarily on cardiac toxicity and cutaneous reactions.

Patients and Methods:

Study design and participants

This prospective randomized open-label research included 135 patients with localized breast cancer who were referred to the medical oncology, radiation, and clinical oncology departments at South Egypt Cancer Institute, Assiut University, from July 2018 to January 2024. This research received approval from the Ethical Committee of South Egypt Cancer Institute, Assiut University, in accordance with the Declaration of Helsinki SECI-IRB IORG0006563.

The inclusion criteria were histologically confirmed invasive breast cancer without distant metastases, patients aged 18 years and older, an ECOG Performance Scale score of 0-2, and normal cardiac and pulmonary functioning. Adequate hematological, renal, and hepatic function tests were necessary.

The exclusion criteria were distant metastases, contraindications to radiation, poor performance status (3-4), uncontrolled hypertension and diabetes mellitus, decompensated heart failure, and chronic pulmonary conditions.

Randomization:

A computer-generated random number was used to allocate patients to one of the two adjuvant therapies; arm (A) (Conv-RT) who received Trastuzumab with conventional radiotherapy group or arm (B) (Hypo-RT) who received Trastuzumab with Hypo-RT using the closed envelopes approach as outlined below.

Procedures

All patients underwent breast conservative surgery (BCS) or breast radical mastectomy (MRM)

Adjuvant chemotherapy (AC)

All the patients received the AC regimen which include doxirubcin and cyclophosphamide followed by a taxane drug (paclitaxel or docetaxel) prior to the start of radiation, and median duration from last chemotherapy cycle to start of radiation was 4 weeks. Trastuzumab was added during the taxane treatment because trastuzumab with the anthracyclin may be harmful to the heart. Trastuzumab was given every three weeks in a dose of 6mg/m2 for 12months.

Adjuvant radiotherapy

Patients in arm (A) underwent conventional radiation therapy, which comprised 50 Gy delivered in daily fractions of 2 Gy to the entire breast using two tangential fields, along with a boost of 10-16 Gy to the tumor bed for conservative breast cancer. In the case of mastectomy, standard radiation therapy involved 50 Gy administered in daily fractions of 2 Gy to the chest wall using two tangential fields. If lymph nodes are positive, an extra supraclavicular field was administered. Patients were conventionally positioned supine on an inclined breast board with one or both arms elevated above the head.

The remaining patients assigned to Arm B received Hypo-RT, consisting of 42 Gy administered in daily fractions over 16 sessions, or 40 Gy delivered in daily fractions over 15 sessions, with the same approach.

Evaluation of toxicity

Cardiac function was evaluated using echocardiography, assessing left ventricular ejection fraction (LVEF) before the initiation of trastuzumab (post-anthracycline treatment) and regularly every three months until the conclusion of trastuzumab therapy. Trastuzumab will cease at one of the below points: Clinical manifestations indicate congestive heart failure or a definitive reduction in LVEF of 10% or more below the lower limit of normal, or over 15% below baseline levels.

Assessment of skin toxicity, including irritation, discomfort, pruritus, peeling, dry desquamation, and wet desquamation, before to and during radiation. Fatigue was evaluated before to and after radiation treatment.

Follow-up: All patients were evaluated weekly throughout radiation and every three months after completing Trastuzumab for the first two years. Patients were evaluated biannually from years 3 to 5. Furthermore, patients were advised to return if they encountered atypical symptoms.

Statistical Analysis

The statistical analysis was performed using SPSS v26 (IBM Inc., Chicago, IL, USA). Quantitative data were expressed as mean and standard deviation (SD) and compared between the two treatment groups using an unpaired Student's t-test. Qualitative variables were evaluated using the Chi-square test or Fisher's exact test where applicable, and results were presented as frequency and percentage (%).

The Kaplan-Meier method was used to analyze the data. Statistical significance was determined when the two-tailed P value was less than 0.05.

Results:

Clinicopathological characteristics

A total of 150 individuals with localized breast cancer were recruited. Arm A (Conv-RT) included 100 patients, whereas arm B (Hypo-RT) had 50 patients. The median follow-up duration was 34 months (range: 13-90 months) for Conv-RT and 31 months (range: 13-89 months) for Hypo-RT. In both Conv-RT and Hypo-RT groups, invasive ductal carcinoma (IDC) was the most common histology, occurring in 95% and 96% of cases, respectively. The majority of patients in both groups had stage II illness, with 53% in the Conv-RT group and 56% in the Hypo-RT group. The predominant cardiac risk variables were a BMI over 30 (50% against 47%), hypertension (50% versus 41%), hyperlipidemia (46% versus 36%), and diabetes mellitus (24% vs 22%), all substantially elevated in Hypo-RT compared to Conv-RT ($p < 0.001$). The clinicopathological features are detailed in Table 1.

Treatment characteristics

Patients in Hypo-RT arm had significant utilization of BCS (86% vs. 63%, $p <0.001$) and adjuvant chemotherapy (68% vs. 43%, $p <0.001$), mainly anthracycline based chemotherapy (62% vs. 41%, $p <0.001$) compared with Conv-RT arm. Regarding radiation therapy parameters, there is no significant difference in the radiation dose fractions in both groups ($p=0.550$). Similarly, no significant difference in the mean heart dose (cGY) between the two arms ($p=0.88$). However, there is a significant difference in radiation field design, with more patients in the conventional RT group receiving 3-4 fields (75% vs. 12%, $p<0.001$). Detailed treatment characteristics are described in the table 2.

Cardiac toxicity (LVEF changes)

There was no significant differences between the Conv-RT and Hypo-RT groups regarding baseline and final LVEF with both groups maintaining similar LVEF values throughout the study period ($p=0.89$ and $p=0.98$, respectively). There is no significant difference in the reduction of LVEF from baseline between the groups ($p=0.080$), with the majority of patients in both groups showing a reduction of less than 10%. Cardiac toxicity, whether asymptomatic or symptomatic, is also comparable between the two groups ($p=0.203$). Detailed changes in LVEF and frequency of Cardiac toxicities are described in the table 3

Other toxicities

All non-cardiac toxicities were acute and only grade I-II with the exception of lymphedema. There was significantly lower incidence acute skin toxicity (10% versus 27%, $p = 0.017$) in Hypo-RT compared with Conv-RT. Moreover, there were non-significantly lower incidence of fatigue (2% versus 7%, $p = 0.199$), breast pain (4% versus 10%, $p = 0.691$) with equal percentage of lymphedema cases (2%, $p = 1$) in Hypo-RT compared with Conv-RT, respectively. Treatment related non-cardiac toxicities are described in table 4.

Table1: Baseline characteristics between the studied groups

	Hypofractionated-RT	Conventional –RT	P value
No of the patient	50	100	0.05
Age (median)	53 (37-78%)	54 (30-80%)	0.32
Breast laterality	Left 25 (50%)	55(55%)	0.78
	Right 25 (50%)	45(45%)	
Histology			1
IDC	48 (96%)	95 (95%)	
ILC	2 (4%)	5 (5%)	
Stage			0.4
IA	8 (16%)	9(9%)	
IB	10 (20%S)	10(10%)	
IIA	25(50%)	26(26%)	
IIB	3(6%)	27(27%)	
IIIA	3(6%)	15(15%)	
IIIB	3(6%)	9(9%)	
IIIC	0(0%)	4(4%)	
Hormonal			0.6
Positive	23(46%)	53(53%)	
Negative	27(54%)	47(47%)	
Cardiac risk factors			**<0.001**
BMI >30	25 (50%)	47 (47%)	
Hypertension	25 (50%)	41 (41%)	
Hyperlipidemia	23 (46%)	36 (36%)	
Diabetes	12 (24%)	22 (22%)	
CAD	10 (20%)	16 (16%)	
Family history of	3 (6%)	5 (5%)	
breast cancer	5 (10%)	2 (2%)	
Follow up (months) median (range)	**31** (13-89)	**34** (13-90)	**0.24**

Data are presented as frequency (percentage) or median (range). IDC: invasive ductal carcinoma; ILC: invasive lobular carcinoma; BMI: body mass index; CAD: coronary artery disease. $p\leq 0.05$ is significant.

Table 2: Treatment-related characteristics for patients who used trastuzumab concurrent with radiotherapy.

	Hypo fractionated RT	Conventional RT	P value
Type of surgery			**<0.001**
Breast conservative	43 (86%)	63 (63%)	
Mastectomy	7 (14%)	37 (37%)	
Systemic therapy			
Neoadjuvant therapy	18 (36%)	57(57%)	
Anthracycline based chemotherapy	6 (12%)	20(20%)	
Taxans based chemotherapy	12(24%)	37(37%)	**<0.001**
Trastuzumab with Neoadjuvant chemotherapy	18(36%)	57(57%)	
Adjuvant therapy	34(68%)	43(43%)	
Anthracycline based chemotherapy	31(62%)	41(41%)	
Taxans based chemotherapy	3(6%)	14(14%)	
Trastuzumab with Neoadjuvant chemotherapy	34(68%)	27(27%)	**<0.001**
Endocrine therapy	24(48%)	53(53%)	**<0.001**
Radiation therapy parameter			
Whole breast Fraction scheme			
4005 cGY in15 Fraction	18(36%)		
4256 cGY in 16 Fraction	32(64%)	(100%)	0.550
5000 cGY in 25 Fraction	0(0%)		
Boost	43(86%)	63(63%)	
Median does cGY	1000	1000	**0.004**
Range	(100-1332-800-1600)	(100-1332-800-1600)	
Radiation field design			
2 fields	44(88%)	25(25%)	**<0.001**
3-4 fields	6(12%)	75(75%)	
Mean heart does(cGY)	100	162	0.88
V5(%)	1,3	4,2	0.81
V10(%)	0,2	0,8	0.97
V20(%)	0,1	0,2	0.95

Data are presented as frequency (percentage) or median (range).

Table3: Change in LVEF and frequency of cardiac toxicity

	Hypofractionated RT	**Conventional RT**	**P value**
Baseline LVEF (%)			
Median	61	62	0.89
Range	(50-80)	(51-75)	
Final LVEF (%)			0.98
Median	59	58	
Range	(56-70)	(50-75)	
LVEF reduction from baseline n%			0.080
No decrease	22(44)	42(42)	
< 10%	16(32)	40(40)	
10-15%	5(10)	14(14)	
≥16%	3(6)	4(4)	
LVEF cardiac toxicity %			
Asymptomatic	3(6)	4(4)	0.203
Symptomatic	0	0	

Data are presented as frequency (percentage). LVEF: left ventricular ejection fraction

Table 4: Treatment-related non cardiac toxicity

	Hypo fractionated RT	Conventional RT	P value
Skin	5(10%)	26(27%)	**0.017**
Fatigue	1(2%)	7(7%)	0.199
Breast Pain	2(4%)	10(10%)	0.691
Lymphedema	1(2%)	2(2%)	1

Data are presented as frequency (percentage).

Discussion:

Patients with BC have an elevated prevalence of heart illness. In comparison to age-matched controls devoid of cancer. The increase in cardiac risk may be ascribed to breast cancer itself, as well as to breast cancer treatment [11- 14].

Trastuzumab, a humanized monoclonal antibody, has shown enhancement in DFS and OS for patients with HER2-positive BC [15]. Furthermore, the Hypo-RT regimen was designated as the standard of treatment for adjuvant breast cancer patients in the UK, based on the findings of the START and Ontario studies [16]. Furthermore, the association between the cardiotoxicity of both RTH and trastuzumab has not been comprehensively investigated in Hypo-RT. Given that the Hypo-RT protocol has emerged as the standardized adjuvant treatment for BC [10], this study was undertaken to assess the safety of the concurrent administration of trastuzumab with Conv-RT compared to its use with Hypo-RT in Her2/neu-positive BC

In the present investigation, 6% of patients receiving Hypo-RT and 4% receiving Conv-RT had a significant decrease in asymptomatic LVEF, but this difference lacked statistical significance (p=0.203). These results correspond with previous extensive investigations on concomitant irradiation and trastuzumab, which indicated that asymptomatic reductions in LVEF varied from 3.5% to 18.6% [17-20].

Moreover, our findings align with those of a study conducted by Sayan et al., which retrospectively enrolled 141 HER2-positive breast cancer patients who received concurrent trastuzumab and either hypofractionated radiotherapy (41 patients) or conventional radiotherapy (100 patients) between 2005 and 2018. This study reported that 7% of patients undergoing hypofractionated radiotherapy and 5% receiving conventional radiotherapy experienced significant asymptomatic reductions in left ventricular ejection fraction [21]. In the research by Narwariya et al., 60 breast cancer patients were categorized into Hypo-RT (30 patients) and Conv-RT (30 patients) throughout a 20-month period from October 2016 to June 2018, demonstrating no significant difference in cardiotoxicity between the two groups [22].

Concerning additional non-cardiac toxicities, we observed that all were acute and classified as grade I-II, with the exception of lymphedema. Hypo-RT shown a reduced incidence of skin toxicity (10% against 27%), tiredness (2% versus 7%), and discomfort (4% versus 10%), although the occurrence of lymphedema patients remained same at 2% when compared to Conv-RT. The findings align with those of Mai Atef et al., which demonstrated a reduced incidence of acute cutaneous toxicities in Hypo-RT (grade 1: 28.1%, grade 2-3: 15.6%) compared to Conv-RT (grade 1: 52.9%, grade 2-3: 20.6%) [23]. Additionally, Sayan et al. reported similar results, indicating a reduced incidence of acute skin toxicity in Hypo-RT compared to Conv-RT (12% vs 27%, respectively) [21]. Additionally, a meta-analysis performed in 2015, including 23 trials with a cumulative total of 15,353 breast cancer patients, corroborated similar findings. Hypo-RT was linked to a decrease in grade II-III acute cutaneous toxicities compared to Conv-RT, whether administered at 2.5–3.0 Gy per fraction or 5.0–6.5 Gy per fraction [24].A comprehensive meta-analysis including 13 studies with 8,189 breast cancer patients revealed that Hypo-RT correlates with a reduced incidence of acute cutaneous toxicities in comparison to Conv-RT (RR 0.36; 95% CI 0.21–0.62, $I^2 = 20\%$) [25].

Conversely, no late or delayed toxicity were detected in our investigation. This contradicts the findings of the START-A and START-B studies, which included 2236 (749 patients in the Conv-RT arm and 1487 in the Hypo-RT arm) and 2215 (1105 patients in the Conv-RT arm and 1110 in the Hypo-RT arm) participants, respectively. In these studies, the rates of late skin toxicities at 10 years were 21% and 13% in the Hypo-RT arm, respectively, with no statistically significant difference compared to the Conv-RT arm (RR 0.91 [0.76, 1.09]), (RR 0.84 [0.68, 1.04]). [26, 27]. Moreover, Whelan et al. reported late skin toxicities at a 10-year follow-up of 33.2% in the Hypo-RT arm compared to 29.5% in the Conv-RT arm, with no statistically significant changes noted (absolute difference of 3.7 percentage points, 95% CI, −4.9 to 12.1) [28].

The prospective design and thorough cardiac evaluation of the whole study population are the hallmarks of our research. Nonetheless, our investigation was constrained by its restricted sample size, brief follow-up period, and the absence of disease-free and overall survival data.

Conclusion:

Hypo-RT administered concurrently with trastuzumab is safe and feasible with lower incidence of cardiac and skin toxicities compared with conventional

RT in adjuvant breast cancer patients.so, longer follow-up period is needed to determine long term results.

List of abbreviations

HER2; Human epidermal growth factor receptor 2
ECOG; Eastern cooperative oncology group
Conv-RT; Conventional radiotherapy
Hypo-RT; Hypofractionated radiotherapy
BCS; Breast conservative surgery
MRM; Radical mastectomy
AC; Adjuvant chemotherapy
LVEF; Left ventricular ejection fraction
SD; standard deviation
IDC; Invasive ductal carcinoma
ILC; Invasive lobular carcinoma
BMI; Body mass index
CAD; Coronary artery disease

Competing interests

Authors have no relevant financial or non-financial interests to disclose

Authors' contributions

All authors contributed to the study conception and design. Material preparation, data collection and analysis were performed by AMH, AS and AH. The first draft of the manuscript was written by AMH and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript

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