

Neoadjuvant Chemotherapy Plus Denosumab Compared to Chemotherapy Alone in Hormonal Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Premenopausal Breast Cancer Patients

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Abstract

Background: High mRNA expression levels of receptor activator of nuclear factor- κ B (RANK) were linked with several adverse prognostic factors in breast cancer. The present study aims to assess the activity of neoadjuvant chemotherapy combined with denosumab compared to chemotherapy alone in premenopausal patients with hormonal receptors (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer.

Methods: In this single-center randomized phase II study, we enrolled patients with ER Allred score 4 - 8 at diagnostic biopsy with locally advanced either inoperable tumors or tumors that need downsizing to allow for breast conservative surgery (BCS). Enrolled patients were randomized to receive either neoadjuvant chemotherapy (four cycles of epirubicin/doxorubicin with cyclophosphamide and four cycles of docetaxel) with denosumab or the same chemotherapy alone. Patients in the experimental arm received subcutaneous denosumab 120 mg starting with the first chemotherapy cycle and then with every other cycle (total of four doses). Residual cancer burden (RCB) was the primary endpoint.

Results: We recruited 50 patients (26 in control arm, 24 in experimental arm) for the study. Baseline characteristics were balanced between the two arms including age at diagnosis, ER Allred score (≤ 6 vs. > 6), progesterone receptor (PR) status, Ki67 level, clinical T, clinical N, and clinical stage (stage II vs. III). Noteworthy, 86% of patients were node-positive, 44% had cT4 tumors and 80% had ER Allred score > 6 . Two patients in the control arm did not undergo breast surgery (one lost to follow-up, the other had local progression). There was no difference in

the rates of BCS (58.3% in both arms) between the two arms. No difference in RCB between control and experimental arms (RCB 0-1: 25% vs. 20.8%, respectively, $P = 0.73$) was found. Similarly, there were no differences in pathological T stage (pT0-1: 87.5% vs. 70.8%, $P = 0.29$), pathological N stage (N0: 41.7% vs. 29.2%, $P = 0.55$) or pathological stage (41.6% vs. 33.3%, $P = 0.75$). No significant difference in adverse events profiles between the two arms was observed.

Conclusions: Adding denosumab to neoadjuvant chemotherapy was not associated with lower RCB or improved pathological stage in premenopausal HR+/HER2-negative breast cancer patients with comparable rate of BCS. No new safety signals were observed with the addition of denosumab.

Keywords: Breast cancer; Denosumab; Chemotherapy; Neoadjuvant

Introduction

Several reports and meta-analyses highlighted the association of achieving pathological complete response (pCR) after neoadjuvant chemotherapy with improved survival outcome [1, 2]. However, pCR can be achieved only in a limited proportion of patients with hormonal receptors (HR)-positive, human epidermal growth factor receptor 2 (HER2)-negative breast cancer (2-10%), which points to the need to develop new treatment approach in this category of breast cancer [3, 4].

Receptor activator of nuclear factor- κ B (RANK), expressed on the surface of osteoclasts, lymphocytes and dendritic cells [5], enhances osteoclast activity upon binding with the RANK ligand (RANKL), which eventually increases bone resorption [6]. Noteworthy, RANK was found to be expressed in primary breast cancer cells as well [7]. Increased RANK protein expression in breast tumor tissues is linked with increased opportunity to develop bone metastases as well as increased tumor size, positive lymph nodes (LN) and grade III tumors, especially in patients with strong HR-positivity, and premenopausal status [8, 9].

Denosumab is a fully human monoclonal RANKL inhibitor that has high affinity and specificity to RANKL. Several studies demonstrated the activity of denosumab in preventing

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skeletal-related events in different solid tumors [10].

Noteworthy, in a small proof of concept study involving 27 premenopausal breast cancer patients (mostly hormone receptors-positive/HER2-negative), denosumab (120 mg) were given for two doses followed by breast surgery. There was no significant change of Ki67 levels in surgical specimen compared to baseline; however, denosumab induced a significant increase in tumor infiltrating lymphocytes (TILs) [11]. Noteworthy, several studies highlighted that higher TILs level in residual tumors following neoadjuvant chemotherapy is related to improved survival outcome [12, 13].

The present study aims to assess the activity of neoadjuvant chemotherapy combined with denosumab compared to chemotherapy alone in premenopausal patients with HR-positive, HER2-negative breast cancer.

Materials and Methods

Study design and population

This is a randomized non-comparative phase II study, conducted in one hospital in Saudi Arabia. Enrolled patients were randomized to receive either neoadjuvant chemotherapy and denosumab or chemotherapy alone.

Eligible patients were female premenopausal patients, aged ≥ 18 years at diagnosis, with histologically confirmed estrogen receptor (ER)-positive, progesterone receptor (PR)-positive or negative/HER2-negative breast cancer, with no evidence of metastasis. Enrolled patients had an Allred score for ER 4 - 8 at diagnostic biopsy, with locally advanced inoperable breast cancer, or tumors requiring downsizing to allow for breast conservative surgery (BCS). Patients should have Eastern Cooperative Oncology Group (ECOG) performance status (PS 0 - 2) with adequate liver and renal functions. Exclusion criteria included patients with clinically significant cardiac disease, those with ejection fraction (EF) $< 50\%$, significant comorbidities that, in the judgment of the treating physician, rendered the patient not candidate for the trial, and those with concomitant malignancies within the past 5 years before enrolment, except for adequately treated basal cell carcinoma of the skin or *in situ* carcinoma of the cervix uteri. Patients need to have dental clearance prior to starting denosumab

Treatment regimens

Experimental arm included denosumab 120 mg subcutaneous given every 6 weeks starting from the first cycle (total of four doses). Chemotherapy regimen included doxorubicin, cyclophosphamide (AC) or epirubicin, cyclophosphamide (EC) for four cycles followed by docetaxel for four cycles every 3 weeks. All patients received oral supplementation of calcium (1,000 mg/day) and vitamin D (at least 800 IU) daily. Control arm included the same chemotherapy mentioned above without denosumab. Enrolled patients should receive adjuvant systemic therapy according to the standard guidelines. Adjuvant radiotherapy should be given if indicated by the standard guidelines.

Randomization and treatment allocation

Randomization was automatically performed by electronic CRF system with the use of stratification according to clinical T and N stage (T4 vs. others), (node-positive vs. node-negative). Allocation was web-assisted through the Dendrite System which was programmed to minimize differences between the groups by taking all the stratification factors mentioned into consideration.

Study endpoints

The primary end point was residual cancer burden (RCB) in the surgical specimens, including breast and LN, assessed according to RCB calculator developed by MD Anderson Cancer Center [14]. Secondary endpoints included pCR, defined as pT0/Tis, N0 in the surgical specimen after neoadjuvant chemotherapy, in addition to systemic treatment toxicity assessed according CTCAE v.4.

Statistical analysis

In this randomized phase II study using Fleming's single stage design; we planned to recruit 50 patients based on RCB 0-1 of 15% with neoadjuvant chemotherapy, in HR+, HER2-negative patients enrolled in NEOPAL study [15]. The study will be considered positive in case of RCB 0-1 $\geq 25\%$ and negative if RCB 0-1 $\leq 15\%$ in the experimental arm. In this pilot study, 25 patients were recruited in each arm, based on an alpha error of 0.05, a beta error of 0.2, and a power of 80%.

Data were exported from the electronic data capture system and analyzed using SPSS version 21.0. Percentages were used to describe categorical variables. The RCB was compared between the two treatment groups using the Chi-square test.

Ethical statement

The study was conducted in concordance with the principles of the "Declaration of Helsinki". The study adhered to the principles outlined in the "Guideline for Good Clinical Practice" ICH Tripartite Guideline (January 1997) and complied with local laws. Subjects have given their informed consent, and the study protocol has been approved by the Institutional Review Board committee on human research.

Results

Trial oversight

Between December 2020 and June 2023, we recruited 50 patients (26 in control arm, 24 in experimental arm). Different baseline characteristics were balanced between the two arms, including age at diagnosis, ER Allred score (≤ 6 vs. > 6), PR status, Ki67 level, clinical T, clinical N stage, and clinical stage

(stage II vs. III). Noteworthy, 86% of patients were node-positive, 44% had cT4 tumors, 80% had ER Allred score > 6 and 73.2% had Ki 67 > 20% (Table 1). Two patients in the control arm did not undergo breast surgery (one was lost to follow-up, and the other had local progression). No difference was found in the rate of BCS (58.3% in both arms) (Table 2).

Overall, the rate of pCR was low (4.2%) and rate of RCB 0-1 was 22.9%. No difference in RCB between control and experimental arms was found (RCB 0-1: 25% vs. 20.8%, respectively, $P = 0.73$). Similarly, there were no differences in pathological T-stage (pT0-1: 87.5% vs. 70.8%, $P = 0.29$), pathological N-stage (N0: 41.7% vs. 29.2%, $P = 0.55$), or pathological stage (41.6% vs. 33.3%, $P = 0.75$) (Table 2). No difference in RCB between control and experimental arms in the subgroup analysis was observed (Table 3).

Toxicity

Dose reduction of chemotherapy was performed in 14 and nine patients in the control and experimental arms, respectively. Meanwhile, chemotherapy cycle was delayed in three and two patients, respectively. All patients received the assigned cycles of chemotherapy except for two patients in the control arm (one cycle of docetaxel was omitted in each patient due to peripheral neuropathy).

Nausea/vomiting, stomatitis and fatigue were the most common non-hematological side effects. No significant differences in adverse events profiles were noted between the two arms (Table 4).

Discussion

Neoadjuvant chemotherapy is frequently utilized in premenopausal patients with HR-positive, HER2-negative breast cancer. However, the rate of pCR is still low with current chemotherapy regimens, which highlights the need to develop new systemic treatment strategies. In a meta-analysis of the ABCSG-18 and D-CARE studies involving 7,929 patients, adjuvant denosumab improved disease-free survival in HR-positive/HER2-negative patients, but not in the overall population [16]. Noteworthy, evidence of therapeutic benefit of adding denosumab to neoadjuvant chemotherapy is lacking [11].

In our pilot study, adding four doses of denosumab (120 mg) with every other cycle of neoadjuvant chemotherapy failed to reach the pre-specified rate of RCB 0-1. Notably, RCB 0-1 was numerically lower in the denosumab arm. In addition, no differences were observed in the rate of BCS between the two arms, despite that patient with strong ER-positive/HER2-negative disease, who are more likely to be RANKL-positive, were recruited.

Similarly, in the GeparX trial, which included different subtypes of breast cancer treated with neoadjuvant nab-paclitaxel followed by EC chemotherapy, the addition of denosumab to neoadjuvant nab-paclitaxel did not improve invasive disease-free survival (iDFS) or pCR rate compared to nab-paclitaxel alone. Denosumab was given at a dose of 120 mg

every 4 weeks for six doses [17]. In addition, adding denosumab did not increase disseminated tumor cells eradication compared to chemotherapy alone [18].

D-BEYOND is a prospective, phase IIa, single-arm, multicenter study assessing the effect of denosumab in premenopausal women with early breast cancer. Patients received only two doses of denosumab followed by surgery. The result was also negative.

Collectively, these results highlight that adding denosumab does not improve the outcome of neoadjuvant chemotherapy, and alternative strategies should be investigated. Recently, the addition of the checkpoint inhibitors nivolumab and pembrolizumab to chemotherapy improved pCR rate in HR+/HER2-negative breast cancer in the CheckMate-7FL and KEYNOTE-756 trials, respectively; however, survival data are still awaited [19, 20].

The discrepancy of the benefit of adding denosumab in neoadjuvant setting seen in these trials, and positive result in the adjuvant setting seen in ABCSG-18 and D-CARE studies, may be due to the large number of patients included and also long durations - every 6 months for 5 years in ABCSG-18, and for about 6 months then every 12 weeks for a total duration of 5 years in D-CARE study.

Our study is limited by the small number of patients and administration of only four doses of denosumab, every 6 weeks (to be synchronized with 3-weekly chemotherapy schedule). However, the potential optimal schedule and number of doses of denosumab with chemotherapy are not well defined.

In conclusion, neoadjuvant denosumab did not improve therapeutic outcomes or BCS rate when added to systemic chemotherapy in HR+/HER2-negative premenopausal breast cancer patients. Although the negative result may help indicate that combining denosumab with chemotherapy is unlikely to be beneficial in this patient population, the small sample size limits the generalizability and scientific impact of the findings.

Alternative therapeutic approaches should be assessed to improve the outcomes of neoadjuvant therapy in those patients.

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Conflict of Interest

Shereef Ahmed Elsamany has received honoraria and research grant from Amgen, and honoraria from MSD, Novartis, and AstraZeneca. Omima Elemam has received honoraria from AstraZeneca. Aboelkhair Algahami has received honoraria from

Table 1. Baseline Characteristics Between the Two Groups

Parameters	Control (n = 26)	Experimental (n = 24)	Total	P value
Age at diagnosis				
≤ 40 years	10 (38.5%)	8 (33.3)	18 (36)	0.77
> 40 years	16 (61.5%)	16 (66.7%)	32 (64.0%)	
Pathological type				
Invasive ductal carcinoma	24 (92.3%)	24 (100.0%)	48 (96.0%)	0.49
Others	2 (7.7%)	0 (0.0%)	2 (4.0%)	
ER%				
ER ≤ 50%	4 (15.4%)	4 (16.7%)	8 (16.0%)	0.92
ER > 50%	22 (84.6%)	20 (83.3%)	42 (84.0%)	
Allred score				
4 - 6	6 (23.1%)	4 (16.7%)	10 (20.0%)	0.73
> 6	20 (76.9%)	20 (83.3%)	40 (80.0%)	
PR status				
Negative	4 (15.4%)	5 (20.8%)	9 (18.0%)	0.72
Positive	22 (84.6%)	19 (79.2%)	41 (82.0%)	
PR%				
PR ≤ 50%	12 (46.2%)	14 (58.3%)	26 (52.0%)	0.41
PR > 50%	14 (53.8%)	10 (41.7%)	24 (48.0%)	
Ki67				
≤ 20%	6 (30.0%)	5 (23.8%)	11(26.8%)	0.73
> 20%	14 (70.0%)	16 (76.2%)	30 (73.2%)	
ECOG performance status (PS)				
0	26 (100.0%)	21 (87.5%)	47 (94.0%)	0.1
1	0 (0.0%)	3 (12.5%)	3 (6.0%)	
Clinical-T				
T1	1 (3.8%)	0 (0.0%)	1 (2.0%)	0.46
T2	9 (34.6%)	13 (54.2%)	22 (44.0%)	
T3	3 (11.5%)	2 (8.3%)	5 (10.0%)	
T4	13 (50.0%)	9 (37.5%)	22 (44.0%)	
Clinical T-categories				
T1-3	13 (50.0%)	15 (62.5%)	28 (56.0%)	0.41
T4	13 (50.0%)	9 (37.5%)	22 (44.0%)	
Clinical N-categories				
NX	1 (3.8%)	0 (0.0%)	1 (2.0%)	0.37
N0	4 (15.4%)	3 (12.5%)	7 (14.0%)	
N1	21 (80.8%)	18 (75.0%)	39 (78.0%)	
N2	0 (0.0%)	1 (4.2%)	1 (2.0%)	
N3	0 (0.0%)	2 (8.3%)	2 (4.0%)	
Clinical N-categories				
Negative	4 (15.4%)	3 (12.5%)	7 (14.0%)	0.77
Positive	22 (84.6%)	21 (87.5%)	43 (86.0%)	
Clinical stage				
II	11 (42.3%)	12 (50.0%)	23 (46.0%)	0.78
III	15 (57.7%)	12 (50.0%)	27 (54.0%)	

ER: estrogen receptor; PR: progesterone receptor; ECOG: Eastern Cooperative Oncology Group.

Table 2. The Main Different Parameters Between the Two Groups

Parameters	Control, n = 24	Experimental, n = 24	Total	P value
RCB				
0	2 (8.3%)	0 (0.0%)	2 (4.2%)	0.22
I	4 (16.7%)	5 (20.8%)	9 (18.8%)	
II	12 (50.0%)	8 (33.3%)	20 (41.7%)	
III	6 (25.0%)	11 (45.8%)	17 (35.4%)	
RCB				
0-I	6 (25.0%)	5 (20.8%)	11 (22.9%)	0.73
II-III	18 (75.0%)	19 (79.2%)	37 (77.1%)	
Type of surgery				
BCS	14 (58.3%)	14 (58.3%)	28 (58.3%)	1.0
MRM	10 (41.7%)	10 (41.7%)	20 (41.7%)	
Pathological-T				
T0	4 (16.7%)	3 (12.5%)	6 (14.6%)	0.43
T1	17 (70.8%)	14 (58.3%)	31 (64.6%)	
T2	3 (12.5%)	5 (20.8%)	8 (16.7%)	
T3	0 (0.0%)	2 (8.3%)	2 (4.2%)	
Pathological T-categories				
T0-1	21 (87.5%)	17 (70.8%)	38 (79.2%)	0.29
T2-3	3 (12.5%)	7 (29.2%)	10 (20.8%)	
Pathological N-categories				
N0	10 (41.7%)	7 (29.2%)	17 (35.4%)	0.74
N1	9 (37.5%)	9 (37.5%)	18 (37.5%)	
N2	4 (16.7%)	6 (25.0%)	10 (20.8%)	
N3	1 (4.2%)	2 (8.3%)	3 (6.3%)	
Pathological node				
Negative	10 (41.7%)	7 (29.2%)	17 (35.4%)	0.55
Positive	14 (58.3%)	17 (70.8%)	31 (64.6%)	
Pathological stage				
0-I	10 (41.6%)	8 (33.3%)	15 (31.3%)	0.75
II-III	14 (58.4%)	16 (66.7%)	33 (68.8%)	
Pathological stage				
0	2 (8.3%)	0 (0.0%)	2 (4.2%)	0.50
I	8 (33.3%)	8 (33.3%)	16 (33.3%)	
II	8 (33.3%)	7 (29.2%)	15 (31.3%)	
III	6 (25.0%)	9 (37.5%)	15 (31.3%)	

BCS: breast conservative surgery; RCB: residual cancer burden.

MSD and Astrazeneca. Faiza Hassanin, Hossam Alghanmi, and Khaled Abd Elaziz El naghi have no conflict of interest to disclose.

Informed Consent

Informed consent was obtained.

Author Contributions

All authors have contributed significantly to the research work. Shereef Ahmed Elsamany and Khaled Abd Elaziz Ahmed El naghi conceived of the presented idea. Khaled Abd Elaziz Ahmed El naghi, Hossam Alghanmi and Aboelkhair Algahami collected the clinical data. Omima Elemam and Faiza Hassanin verified the analytical methods, analysis and interpretation of

Table 3. Subgroup Analysis for RCB

Parameters	Control, n = 26		Experimental, n = 24		P value
	RCB 0-1	RCB	RCB 0-1	RCB	
Age					
≤ 40 years	6 (23%)	6 (23%)	0	8 (33%)	0.072
> 40 years	3 (11%)	12 (46%)	5 (20%)	11 (50%)	0.47
Allred score					
4 - 6	1 (3.8%)	5 (19%)	0	4 (16%)	0.39
> 6	5 (19%)	13 (50%)	5 (20%)	15 (62%)	0.84
PR status					
Negative	0	3 (11%)	2 (8%)	3 (12%)	0.21
Positive	6 (23%)	15 (57%)	3 (12%)	16 (66%)	0.33
Ki67					
≤ 20	2 (7%)	4 (15%)	0	5 (20%)	0.15
> 20	3 (11%)	9 (34%)	5 (20%)	11 (50%)	0.72
Clinical T-categories					
T1-3	4 (15%)	8 (30%)	4 (16%)	11 (50%)	0.71
T4	2 (7%)	10 (38%)	1 (4%)	8 (33%)	0.72
Clinical N-categories					
Negative	0	3 (11%)	0	3 (12%)	-
Positive	6 (23%)	15 (57%)	5 (20%)	16 (66%)	0.73
Clinical stage					
II	5 (19%)	5 (19%)	4 (16%)	8 (33%)	0.43
III	1 (3.8%)	13 (50%)	1 (4%)	11 (50%)	0.91

RCB: residual cancer burden; PR: progesterone receptor.

data. Shereef Ahmed Elsamany and Khaled Abd Elaziz Ahmed El naghi wrote the manuscript with support from Omima Elmam and Aboelkhair Algahami. All authors contributed to the review and editing of the manuscript.

Data Availability

The datasets generated during and/or analyzed during the cur-

rent study are available from the corresponding author on reasonable request.

Abbreviations

BCS: breast conservative surgery; AC: doxorubicin, cyclophosphamide; EC: epirubicin, cyclophosphamide; HR: hormonal receptors; iDFS: invasive disease-free survival; pCR:

Table 4. The Adverse Events Profiles Between the Two Groups

Adverse events type	Control			Denosumab		
	Incidence	Grade 1/2	Grade 3/4	Incidence	Grade 1/2	Grade 3/4
Vomiting	5 (20%)	4 (16%)	1 (4%)	7 (28%)	3	4 (16%)
Nausea	10 (40%)	10 (40%)	0	7 (28%)	7 (28%)	0
Hypocalcemia	1 (4%)	1 (4%)	0	4 (16%)	4 (16%)	0
Constipation	4 (16%)	4 (16%)	0	4 (16%)	4 (16%)	0
Fatigue	12 (48%)	8 (32%)	4 (16%)	11 (44%)	10 (40%)	1 (4%)
Stomatitis	9 (36%)	7 (28%)	2 (8%)	10 (40%)	9 (36%)	1 (4%)
Skin inflammation	4 (16%)	4 (16%)	0	5 (20%)	4 (16%)	1 (4%)
Neuropathy	6 (24%)	6 (24%)	0	4 (16%)	4 (16%)	0

pathological complete response; RANKL: RANK ligand; RANK: receptor activator of nuclear factor- κ B; RCB: residual cancer burden

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