Neoadjuvant Therapy with Doxorubicin-Cyclophosphamide Followed by Weekly Paclitaxel in Early Breast Cancer: A Retrospective Analysis of 200 Consecutive Patients Treated in A Single Center with A Median Follow-Up of 9.5 Years.

Lisi M. Dredze

Ben-Gurion University of the Negev Faculty of Health Sciences

Michael Friger

Ben-Gurion University of the Negev Faculty of Health Sciences

Samuel Ariad

Ben-Gurion University of the Negev Faculty of Health Sciences

Michael Koretz

Soroka University Medical Center: Soroka Medical Center

Bertha Delgado

Ben-Gurion University of the Negev Faculty of Health Sciences

Ruthy Shaco-Levy

Ben-Gurion University of the Negev Faculty of Health Sciences

Margarita Tokar

Soroka University Medical Center: Soroka Medical Center

Michael Bayme

Ben-Gurion University of the Negev Faculty of Health Sciences

Ravit Agassi

Soroka University Medical Center: Soroka Medical Center

Maia Rosenthal

Soroka University Medical Center: Soroka Medical Center

Victor Dyomin

Soroka University Medical Center: Soroka Medical Center

Olga Beluchitski

Soroka University Medical Center: Soroka Medical Center

Shai Libson

Soroka University Medical Center: Soroka Medical Center

Tamar Mizrahi

Ben-Gurion University of the Negev Faculty of Health Sciences

David B. Geffen (✉ dgeffen@bgu.ac.il)

Soroka University Medical Center: Soroka Medical Center <https://orcid.org/0000-0003-0489-2870>

Research Article

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Abstract

Purpose

We analyzed outcomes of doxorubicin-cyclophosphamide(AC) followed by weekly paclitaxel as neoadjuvant chemotherapy(NAC) for breast cancer(BC), in an everyday practice with long-term follow-up of patients.

Methods

All patients (n=200) who received the AC-paclitaxel combination as NAC for BC at the Soroka University Medical Center from 2003 to 2012 were included in this retrospective cohort study. AC was administered on an every 3-week schedule (standard dose) until May, 2007(n=99); and subsequently every 2 weeks (dose dense)(dd)(n=101). Clinical pathologic features, treatment course and outcome information were recorded. Complete pathologic response(pCR) was analyzed according to BC subtype, dose regimen and stage.

Results

Median age was 49 years; 55.5% and 44.5% of patients were clinically stage 2 and 3, respectively. Standard dose patients had more T3 tumors. Subtypes were human-epidermal-growth-factor receptor(HER 2)-positive 32.5% (of whom 82% received trastuzumab), hormone-receptor positive/HER2 negative 53%, triple negative 14.5%. Breast conserving surgery(BCS) was performed in 48.5% of patients; only 9.5% were deemed suitable for BCS prior to NAC. Toxicity was acceptable. The overall pCR rate was 26.0% and was significantly higher in the dd group and HER2-positive patients. With a median follow-up of 9.51 years median event-free survival(EFS), and overall survival(OS) is 10.85 years and 12.61 years, respectively. Patients achieving pCR had significantly longer EFS and OS.

Conclusions-

NAC for BC with AC-paclitaxel can be safely administered in the “real-world” setting with high efficacy. Current efforts are aimed at increasing rates of pCR and identifying patients who may benefit from additional therapy or conversely, de-escalated treatment.

Introduction

Neoadjuvant(preoperative) chemotherapy(NAC) facilitates breast conservation surgery(BCS) in operable breast cancer(BC) and enables mastectomy with clear margins in locally advanced BC [1]. The achievement of complete pathologic response (pCR) as evaluated at surgery after NAC has been shown to correlate with improved event-free survival (EFS) in two BC subtypes: triple negative (TN)(negative for estrogen-receptor (ER), progesterone- receptor (PR), and human-epidermal-growth-factor-2 receptor (HER2) overexpression) and HER2-positive [2,3]. Recently it was shown that in these two subtypes, pCR can serve as a predictive marker to guide selection of subsequent adjuvant therapy [4,5]. Doxorubicin-cyclophosphamide (AC) has been administered as adjuvant and neoadjuvant therapy of BC for more than 3 decades [6]. The addition of a taxane to NAC regimens was shown to increase the rate of pCR and overall survival (OS) as did shortening the treatment interval between cycles of AC from 3 weeks to 2 weeks (dose-dense(dd) therapy) [7-9]. For patients with HER2-positive tumors, the anti-HER2 receptor monoclonal antibody trastuzumab improves EFS and has been a component of neoadjuvant regimes since 2005. In 2014 pertuzumab was added, a monoclonal antibody inhibiting the dimerization of the HER2 receptor [10-12].

Seven recent reports have demonstrated the effectiveness of NAC in BC outside of clinical trials. The longest median follow-up was 7.4 years (13). In two studies, treatment regimen was not reported and in the others the NAC administered, although mostly anthracycline-taxane based, varied in specific drugs and schedules used [13-19]. The AC-paclitaxel regimen is recommended by the National Comprehensive Cancer Network as a preferred combination for HER2-negative breast cancer and as “useful under certain circumstances” in HER2 positive disease [20]. To the best of our knowledge there are no “real-world” studies of AC-

paclitaxel given as a single uniform NAC protocol in a cohort of patients with complete hormone and HER2 receptor data, with long-term follow-up.

In 2003 our center adopted the AC - weekly paclitaxel regimen as the standard neoadjuvant regimen for BC patients. In 2007 we shortened the interval between cycles of AC from 21 to 14 days with granulocyte-colony stimulating factor(G-CSF) support. The purpose of the study presented here was to evaluate the efficacy and toxicity of AC-weekly paclitaxel as NAC in patients with stage II-III BC, treated in a non-clinical trial setting with a median follow-up of 9.5 years. The primary endpoint of interest was the achievement of pCR, with secondary endpoints of EFS, OS, and distant disease-free survival (DDFS). In addition, we wanted to evaluate the impact of dose regimen (standard vs. dd), tumor subtype, body mass index (BMI), and pre-chemotherapy neutrophil-lymphocyte ratio (NLR) on EFS, DDFS, OS and achieving pCR.

Patients And Methods

Soroka University Medical Center(SMC) is a 1150-bed tertiary level hospital, and its Cancer Center provides comprehensive oncology care to most of the one million residents of southern Israel. All citizens receive government mandated universal health care coverage via one of 4 Health Funds, and there has been an active free breast cancer screening program nationally in place since the early 1990's [21].

We performed a retrospective cohort study of patients with newly diagnosed stage II-III BC treated with neoadjuvant AC-paclitaxel chemotherapy at SMC from 2003 to 2012. Inclusion criteria included treatment with at least one dose of AC-Taxol; excluded were patients with metastatic disease at diagnosis. Requirements for receiving the NAC protocol included normal laboratory values for complete blood count, renal and liver function as well as a left ventricular ejection fraction of 50% or above as determined by echocardiogram or multi-gated acquisition cardiac scan. Decision to administer AC-paclitaxel (the standard NAC) was made jointly by the attending oncologist and breast surgeon. Patients underwent mammography, breast ultrasound, core biopsy and appropriate imaging studies. In addition to the histologic diagnosis, immunohistochemistry (IHC) stains were performed on biopsy specimens to evaluate ER, PR, and HER2. When indicated for further evaluation of HER2 status, fluorescent(FISH) or chromogen-in-situ hybridization (CISH) was performed. Final determination of HER2 status was as per standard guidelines at the time [22]. Patients who were diagnosed from 2003 through 2007 received treatment according to the standard treatment cycle interval- four cycles of AC (doxorubicin 60mg/m² cyclophosphamide 600mg/m²) every three weeks followed by 12 weekly doses of paclitaxel (80mg/m²). Between May and December,2007 the dd protocol was phased in and from 2008 until the end of the study period all patients except for one were treated with the dd protocol. One to two months following NAC, all patients underwent definitive surgical treatment – mastectomy or BCS- along with sentinel node biopsy and/or axillary node dissection. Post-operative radiotherapy (RT) to the breast/chest wall and supraclavicular/high axillary lymph nodes was administered to almost all patients. ER and/or PR positivity (determined by IHC staining of greater than 1 % of nuclei for ER and PR, respectively) was considered hormone-receptor (HR)-positive. Following RT, HR-positive patients received endocrine therapy with tamoxifen and/or aromatase inhibitors along with ovarian suppression therapy as indicated.

From 2005-2007 patients with overexpression of HER2 determined by IHC staining +3 or IHC +2 that was FISH or CISH positive received adjuvant trastuzumab in the post- operative period every three weeks for one year. Starting in 2007, HER2 positive patients received neoadjuvant trastuzumab weekly along with the weekly paclitaxel in addition to the post-operative trastuzumab for a total of one year of anti-HER2 therapy. No patients in the study received pertuzumab.

Clinical and pathological information was obtained from medical records. Patient data was anonymized before entering onto an electronic data base. Data recorded included age, ethnicity, menopausal status, pretreatment BMI, pretreatment NLR, TNM classification [23], date and type of surgery, degree of differentiation, histology, expression of ER, PR, and HER2 on tumor specimens, clinical and pathologic response, dates of disease recurrence, diagnosis of a second breast or non-breast malignancy, and death from any cause. Patient reported outcomes (PROs) were not collected but grade III and IV toxicities were recorded. When available, the surgeon's initial opinion of the feasibility of BCS without NAC was noted. The clinical response was evaluated at the completion of NAC by physical examination, mammography, breast ultrasound and in some cases magnetic resonance imaging of the breasts. The pathological response was evaluated on the definitive surgical specimen. The definition of pCR was the absence of invasive cancer in the surgical specimens of the breast and axillary lymph nodes [24]. Partial pathologic response

(pPR) was defined as at least a 30% reduction in diameter of the primary tumor. EFS was defined as the time from the date of diagnosis until local or distant recurrence of disease; second breast or other malignancy; or death from any cause. DDFS was considered as the time from date of diagnosis to distant recurrence, second malignancy other than breast cancer, or death from any cause. OS was defined as the time from the date of diagnosis of disease until death from any cause [24,25]. The cut-off date for follow-up was July 1, 2019. The study was approved by the SMC Institutional Review Board.

Statistical Analysis

Quantitative data are presented using means $\pm$ standard deviations (SD) with medians and ranges also shown. Categorical data are presented using percentages. For the two sub-groups (dd vs standard dose) the Chi Square test was used for the comparison of categorical data. Kaplan-Meier survival analysis was used to calculate OS, DDFS and EFS from the date of diagnosis until date of death (OS); and disease recurrence or death (DDFS, EFS). The Log-Rank Test was used to compare univariate points of end of survival. The represented results are “two-tailed” where a p-value less than or equal to 0.05 is considered statistically significant.

Results

During the study period, 200 patients at SMC received AC-paclitaxel NAC (dd, n=101; standard dose, n=99). Dates of diagnosis (breast biopsy) of the first and last patients on the study were April 9, 2003 and May 20, 2012, respectively. Clinicopathologic features of patients are shown in Table 1, according to treatment regimen, and were evenly balanced for age, menopausal status, ethnicity, histologic type, HER2, ER, PR and tumor subtype. Two patients had bilateral breast cancer at diagnosis. Smaller tumors (T-stage) and more clinical stage II patients relative to stage III patients were noted in the dd group, probably due to a decreased threshold in tumor size for recommending NAC in the later years of the study. NLR was increased in the conventional dose group, but 10 % of the values for these patients were missing. BMI data was not available for 16.8 % of the standard dose patients.

Germ-line genetic testing for mutations in the BRCA1 and BRCA2 genes was performed in 24 patients, as indicated by standard of care guidelines at the time. Six patients were found to have BRCA1 mutations, including one patient with both BRCA1 and BRCA2 mutations. Early in the study period, trastuzumab was approved by regulatory agencies in the United States and Israel for use along with chemotherapy in early stage HER2-positive BC, and subsequently also as neoadjuvant therapy. Trastuzumab was given to all HER2-positive patients in the dd cohort but to only 56%(n=15) of the standard dose HER2-positive patients (Table 2).

Achievement of pCR was a key endpoint because of its previously demonstrated association with survival in two of the major subtypes of BC [2,3]. Overall, 52 (26%) out of the 200 patients achieved pCR. Table 3 shows the pCR rate according to treatment cohort, HER2 status, BC subtype, T stage and clinical stage. Most patients in all categories achieved at least a partial response. Complete response was associated with receiving dd NAC and having a HER2-positive subtype of BC. Of patients whose tumors were HER2-positive, 52.3% achieved pCR while only 13.3% of patients with HER2-neg BC achieved pCR ($p<0.001$). Among the 12 HER2-positive patients who did not receive trastuzumab only two had a pCR.

Additional treatment is summarized in Table 4, showing the various standard-of-care endocrine therapies administered to HR-positive patients depending on menopausal status and clinical judgement of the treating oncologist. Almost all patients received post-operative radiotherapy. Of interest, nearly half (48.5%) of the entire cohort underwent BCS, after the surgeon's pre-NAC evaluation had been that a mastectomy was needed in at least 82.5 % of patients (Pre-NAC surgeon's evaluation missing n=16 (8.0%)).

At a median follow-up of 9.51 years(yrs) (range 1.20-16.0) for the entire cohort, as of the cut-off date, 112 (56.0%) patients were alive and event-free. One patient in the dd group was lost to follow-up when she left the country. At her last clinic visit 2.4 yrs after diagnosis she had no evidence of disease. Distant BC metastases occurred in 67 (33.5%) patients, while only 2 patients experienced a local recurrence in the ipsilateral breast. There have been 65 (32.5%) deaths, mostly (n=63) from metastatic BC. One patient died of metastatic renal cell carcinoma 9 yrs after BC diagnosis and one patient died of heart failure 10 yrs after BC diagnosis. There were ten cases of contralateral BC and 10 patients who during follow-up were diagnosed with other malignant diseases including one patient with metastatic BC who developed 2 additional malignancies. Kaplan-Meier survival curves for DDFS, EFS and OS for all patients are shown in Figure 1 a-b-c.

Median DDFS, EFS and OS were 11.2 yrs (95% Confidence Interval (CI) 10.33-12.07 yrs), 10.85 yrs (95% CI 9.97-11.73 yrs), and 12.61 yrs (95% CI 11.88-13.34 yrs), respectively. Five- and 10- year EFS were 69.5 % and 60.5% while for OS the five- and 10-year survivals were 85.0% and 70.0 % respectively.

Survival curves (EFS and OS) for patients according to treatment regimen are shown in Figure 2a-b and by tumor subtype in Figure 3 a-b.

There was no significant difference in EFS or OS between the two treatment groups (logrank= 0.127 and 0.136, respectively). When patients were divided according to tumor subtype (HR-positive/HER2-negative, HER2-positive, TN), EFS and OS were numerically longer in HER2-pos patients versus EFS and OS of the two other subtype groups, but there were no statistically significant differences (logrank for EFS and OS =0.287 and 0.085 respectively).

Figure 4 a-b shows EFS and OS according to the achievement of pCR to NAC.

As expected, patients with a pCR had longer EFS (logrank p=0.009) OS (logrank p=0.007) and DDFS (logrank p= 0.005) as opposed to those without pCR (DDFS not shown).

When broken down into subtypes only the HER2-positive group showed statistically significant better EFS (log rank p=0.038) and DDFS (log rank p=0.030) and a strong trend for improved OS (log rank p=0.056) for the pCR patients as opposed to patients not achieving pCR (Figure 5 a-b, DDFS not shown.)

Toxicity of the NAC in both treatment regimens was acceptable, with one possible treatment related death, the patient who died of heart failure at the age of 58 years, ten years after receiving dd AC-paclitaxel and trastuzumab, with no evidence of BC recurrence. Neutropenia was the most common grade 3-4 toxicity, occurring in 62.4 % of patients on the standard dose regimen but in only 7.1 % of the dd group (all dd patients received G-CSF)(p=0.000). Despite the high rate of neutropenia in the standard dose group, there were only 16 patients (15.8%) who developed neutropenic fever. As shown in Table 5, dose delays, reductions or omissions occurred in 76 (38.0 %) of patients, 35.6% of the standard dose group and 40.4 % of dd patients.

Table 6 shows the distribution of subsequent malignancies by treatment regimen. Ten patients had second (contralateral) BCs and 10 other patients had non-breast neoplasms, evenly divided between the dd and standard dose NAC regimens. Two patients developed post-radiation angiosarcomas, one in the skull after cranial irradiation for brain metastases from BC, and one, with a heterozygous mutation in the ATM gene, in the irradiated breast. Four of the 5 patients with second non-BC malignancies who died during follow-up, also had active metastatic BC.

Discussion

In this retrospective study of 200 stage II and III BC patients treated with doxorubicin and paclitaxel-based NAC with a mean follow-up of 9.5 years, we have shown median EFS and OS of 10.8 and 12.6 years, respectively with a 10-year OS of 70%. Whereas pretreatment evaluation of suitability for breast conservation therapy showed less than 10% of patients meeting criteria for BCS, after NAC 48% of patients underwent BCS. The Early Breast Cancer Trialists' collaborative Group meta-analysis showed no significant differences between adjuvant and NAC for OS or distant recurrence so the high rate of BCS is an important consideration in clinical decision-making (26). The patients in our dd cohort did not have significantly different EFS, DDFS, or OS than pts in the standard dose cohort; but the study was not powered to compare the treatment regimens. There were significantly more episodes of neutropenia in the standard dose cohort but that did not translate into more episodes of hospitalization for neutropenic fever. There were no deaths from neutropenic fever, that in the past might have been expected in chemotherapy studies but now minimized with advances in supportive care particularly in the setting of a comprehensive cancer center.

In the HER2-positive subgroup, the achievement of pCR was correlated with improved EFS and DDFS and a trend for improved OS, as in previous prospective and retrospective reports [3,11,27]. The TN cohort showed a trend for improved results in those pts with pCR. In addition to being a prognostic factor in those two subgroups, clinical trials have shown pCR is predictive of the effectiveness of adding specific adjuvant therapies, now standard, after conclusion of NAC [20]. In the CREATE-X study, where HER2-negative BC patients who received standard NAC and did not achieve pCR were randomized to receive adjuvant

capecitabine or no further treatment the TN patients receiving capecitabine had significantly longer 5- year disease free survival (DFS) HR 0.58 (95 % CI 0.39-0.87) [28]. In the KATHERINE trial HER2-positive patients who did not achieve pCR after standard NAC were randomized to continue with standard adjuvant trastuzumab or to receive the antibody-drug conjugate trastuzumab emtansine. Three-year invasive DFS in the trastuzumab-emtansine group was significantly higher than in the control treatment group, HR 0.50(95 % CI 0.39-0.64) [5].

Over the course of follow-up 10 (5%) of the patients in our series were diagnosed with a non-breast cancer. Second non-breast neoplasms after treatment of primary BC may have several etiologies such as chemotherapy/radiotherapy effects, genetic predisposition to additional malignancies, as well as the background incidence of cancers [29]. Two studies showed an 8-15 % increase in the expected age matched rate of second malignancies after 10 years median follow-up of newly diagnosed BC patients [30,31]. In our study only six patients were known to have germ line deleterious mutations such as BRCA1 or BRCA2 and none of those patients had a second non-breast malignancy. One patient was heterozygous for an ATM mutation and developed two non-BC primaries; angiosarcoma of the ipsilateral breast and uterine cancer 6 and 7 yrs, respectively, after BC diagnosis. Interestingly, a study with a median follow-up of 5 yrs of 91 BC patients heterozygous for pathogenic germ line mutations of ATM, found that there was no increase in the incidence of second malignancies or radiation toxicity [32].

Our results are consistent with those of other published “real-world” experience. Table 7 is a summary of reports we could find of treatment and follow-up of NAC in BC in the non-clinical trial setting. While one study, from Canada, is a population- based study, the other six are hospital based retrospective summaries of experience with NAC, as is ours. The rates of pCR range between 14%-42% with the pCR attained in our trial near the median. Survival data, though not always reported using the same metrics, was similar to what we report. Only two studies besides ours provided information on whether breast conservation was achieved. Our report is the only one where all patients received the same basic protocol, AC-paclitaxel.

Limitations of our study include its retrospective nature and relatively small size. We did not collect PROs. The relatively high number of missing values for NLR and BMI (16.8% and 10% respectively) in the standard dose group precludes substantive analysis but they remain important measures to investigate in predicting response to NAC (33,34). NLR was higher in the standard dose group, perhaps due to the predominance of stage III disease in that group. Obesity is a risk factor for BC, and body-mass index (BMI) has been shown to be correlated in other studies with pCR and survival [34,35]. The immune response, as manifested by increased lymphocyte infiltration is probably an important determinant of response to therapy (36).

Comparisons of the two treatment groups, dd and standard, must be regarded as exploratory since patients received treatment according to the time period in which they presented, without randomization or stratification. There are several strong points in this report: All 200 patients were treated in a single institution with a uniform treatment approach using the same chemotherapy agents for all patients eligible for NAC of BC; IHC staining for ER, PR, and HER2 was performed on all biopsy specimens; details of treatment including the type of breast surgery performed, are known for all patients; and median follow-up is relatively long.

Further refinements under investigation in the neoadjuvant therapy of BC include administering additional drugs, such as carboplatin and the checkpoint inhibitor pembrolizumab in TN BC [37,38]. In HER2-positive BC, neoadjuvant pertuzumab has been standard therapy for several years now, along with trastuzumab [20]; and adjuvant neratinib, given after standard NAC in HR positive HER2 positive, high- risk patients, was shown to increase invasive disease-free survival [39]. The innovative series of I-SPY trials has shown increased pCR rates by adding new agents to the AC-paclitaxel combination such as in HER2-positive patients and a PARP inhibitor, veliparib, with carboplatin, in TN BC [40-42]. RNA expression testing in HR- positive patients shows promise in selecting patients appropriate for neoadjuvant endocrine therapy [43-45]. The addition of CDK4/6 inhibitors to standard endocrine therapy in this subgroup is being investigated [46].

Early prediction of failure to achieve pCR may improve the outlook for such patients by enabling early switching to different or investigational NAC regimens. Approaches being investigated in addition to RNA expression testing to predict the likelihood of achieving pCR include using a nomogram based on contrast enhanced computed tomography of the breast (radiomics), machine learning, and measuring circulating cell-free tumor DNA [47-49]. There are studies to predict which patients will do well with less intensive NAC, such as via measuring early changes in tumor uptake of radiolabeled fluorodeoxyglucose, and efforts to identify those for whom surgery can be omitted [50,51].

Conclusion

Our study has provided evidence that NAC for BC with the AC-paclitaxel combination chemotherapy regimen along with appropriate anti-HER2 therapy, endocrine therapy, RT and surgery, can be safely and effectively administered in the “real-world” setting. This analysis, with its relatively long follow-up, along with other “real-world” reports, yields results that fulfill the promise of clinical trials that introduced this treatment program. Modifications of the NAC approach to further improve outcomes are being investigated such as identifying those BC patients who may benefit from additional and/or more intensive treatment; and those who will do well with less aggressive treatment.

Abbreviations

BMI
body mass index
ER
estrogen receptor
HER2
human epidermal growth factor receptor-2
neg
negative
No
number
pos
positive
PR
progesterone receptor

Declarations

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Conflicts of Interests/Competing interests

None of the authors have any conflicts of interests or competing interests to report.

Availability of Data and Material

The data analyzed in this study is available on reasonable request from the corresponding author.

Code Availability

Not applicable.

Author Contributions: LMD, MF, TM, DBG designed the analysis. SA, MK, MT, MB, RA, OB, SL, and DBG cared for the patients. MF performed the statistical analysis. BD, RSL and VD performed the pathologic analyses. MR interpreted many of the follow-up breast imaging studies and performed biopsies on many of the patients with breast recurrences. LMD, MT, OB, TM and DBG gathered the data. All of the authors participated in writing the manuscript and have approved it.

Ethics approval

This study was approved by the Soroka University Medical Center Institutional Review Board (IRB).

Consent to Participate

Requirement for patient consent waived by the IRB, because of the retrospective nature of the study and the anonymization of patient data.

Consent for publication

Requirement for patient consent for publication waived by the IRB, because of the retrospective nature of the study and the anonymization of patient data.

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Tables

Table 1 Patient Characteristics

	Conventional Dose N(%)	Dose Dense N(%)	Total N(%)	p-value
No. of patients	101 (50.5)	99 (49.5)	200 (100)	
Age				p=0.507
Median (yrs)	49	48	49	
Range (yrs)	23-72	23-66	23-72	
Less than 40 yrs	17 (16.8)	18 (18.2)	35 (17.5)	
40-60 yrs	67 (66.3)	70 (70.7)	137 (68.5)	
60-75 yrs	17 (16.8)	11 (11.1)	28 (14.0)	
Over 75 yrs	0	0	0	
Menopausal Status				p=0.117
Premenopausal	54 (53.5)	54 (54.5)	108 (54.0)	
Postmenopausal	43 (42.6)	34 (34.3)	77 (38.5)	
Perimenopausal/unknown	4 (4.0)	11 (11.1)	15 (7.5)	
Ethnicity				p=0.447
Jewish	92 (91.5)	86 (86.9)	178 (89.0)	
Bedouin/Arab	9 (8.9)	12 (12.1)	21 (10.5)	
Other	0 (0)	1 (1.0)	1 (0.5)	
Clinical T-stage				p=.004
T0	1 (1.0)	1 (1.0)	2 (1.0)	
T1	3 (3.0)	3 (3.0)	6 (3.0)	
T2	29 (28.7)	55 (55.6)	84 (42.0)	
T3	57 (62.0)	35 (38.0)	92 (46.0)	
T4	11 (10.9)	5 (5.1)	16 (8.0)	
Clinical Axillary Node Status				p=0.681
Negative	23 (22.8)	25 (25.3)	48 (24.0)	
Positive	78 (77.2)	74 (74.7)	152 (76.0)	
Clinical Stage				
II	44 (43.6)	67 (67.7)	111 (55.5)	P=.001
III	57 (56.4)	32 (32.3)	89 (44.5)	
Inflammatory Cancer				P=0.783
No	95 (94.1)	94 (94.9)	189 (94.5)	
Yes	6 (5.9)	5 (5.1)	11 (5.5)	
Histologic type				P=0.795
Invasive ductal	87 (86.1)	88 (88.9)	175 (87.5)	

Invasive lobular	11 (10.9)	8 (8.1)	19 (9.5)	
Other	3 (3.0)	3 (3.0)	6 (3.0)	
Histologic Grade at diagnosis	p=0.720			
Low	1 (1.0)	1 (1.0)	2 (1.0)	
Intermediate	8 (7.9)	4 (4.0)	12 (6.0)	
High	18 (17.8)	18 (18.2)	36 (18.0)	
Undetermined	74 (73.3)	76 (76.8)	150 (75.0)	
ER status	P=0.689			
Neg	32 (31.7)	34 (34.3)	66 (33.0)	
Pos	69 (68.3)	65 (65.7)	134 (67.0)	
PR status	P=0.574			
Neg	47 (46.5)	50 (50.5)	97 (48.5)	
Pos	54 (53.5)	49 (49.5)	103 (51.5)	
HER2 status	P=0.079			
Neg	74 (73.3)	61 (61.6)	135 (67.5)	
Pos	(26.7)	38 (38.4)	65 (32.5)	
Tumor subtype	p=0.362			
Luminal-A like (HER2neg /ER pos/PR pos)	47	38	85	
Luminal -B like (HER2 neg/ER pos/PR neg)	9	11	20	
Triple negative (HER2 neg/ERneg/PRneg)	17	12	29	
HER2 pos/ ERneg/PRneg	14	22	36	
HER2pos/ERpos/PR neg	7	5	12	
HER2 pos/ERpos/PR pos	6	11	17	
HER2neg/ ER neg/ PR pos	1	0	1	
BMI-				
< 25	34 (33.7)	39 (39.4)	73 (36.5)	—
25 or >25	50 (49.6)	58 (58.6)	108 (54.0)	
missing	17 (16.8)	2 (2.0)	19 (9.5)	
Neutrophil-Lymphocyte ratio	0.033			
1 st quartile (1.79 or less)	20 (22.0)	27 (27.8)	47 (25.0)	
2 nd quartile (1.80 – 2.28)	21 (23.1)	27 (27.8)	48 (25.5)	

3 rd quartile (2.29 – 2.80)	18 (19.8)	27 (27.8)	45 (23.9)	
4 th quartile (2.81 or greater)	32 (35.2)	16 (16.5)	48 (25.5)	
missing	10	2	12	
Mean	2.6776	2.3286	2.4975	0.042
Standard Deviation	1.20304	1.12870	1.17522	

Abbreviations: BMI=body mass index, ER=estrogen receptor, HER2=human epidermal growth factor receptor-2, neg=negative, No=number, pos=positive, PR=progesterone receptor

Table 2 Use of Trastuzumab in the HER2 positive (N=65) patients

	Conventional dose (N=27)	Dose-dense (N=38)	total
Adjuvant only	7	1	8
Neoadjuvant and adjuvant	8	35	43
Neoadjuvant only	0	2	2
Not given	12	0	53

Table 3 Pathologic Complete Response and overall pathologic response (complete plus partial response) by dose regimen, tumor subtype, and stage

Patient Characteristics (N)	pCR N (%)	Partial pathologic response N (%)	Overall Response N (%)	p-value for pCR
Dose regimen				P=0.019
Standard (101)	19 (18.8)	69 (68.3)	88(87.1)	
Dose dense (99)	33 (33.3)	56 (56.6)	89 (89.9)	
HER2 status				p<0.001
Positive (65)	34 (52.3)			
Negative (135)	18 (13.3)			
Tumor subtype				
HER2 neg /ER pos/PR pos Luminal-A like (85)	6 (7.1)	66(77.6)	72(84.7)	
HER2 neg/ERpos/PRneg (20)	4 (20.0)	14 (70.0)	18 (90.0)	
HER2 neg/ER neg/PR neg Triple negative (29)	8 (27.6)	16 (55.1)	24 (82.8)	
HER2 pos/ER neg/PR neg (36)	25 (69.4)	10 (27.7)	35 (97.2)	
HER2 pos/ER pos/PR neg (12)	6 (50.0)	4 (33.3)	10 (83.3)	
HER2 pos/ER pos/PR pos (17)	3 (17.6)	5 (29.4)	8 (47.1)	
HER2 neg/ER neg/PR pos (1)	0 (0.0)	1 (100)	1 (100)	
Clinical T stage				
T0 (2)	2 (100)	0	2 (100)	
T1 (6)	2 (33.3)	2 (33.3)	4 (66.7)	
T2 (84)	24 (28.6)	49 (58.3)	73 (86.9)	
T3 (92)	21 (22.8)	61 (66.3)	82 (89.1)	
T4 (16)	3 (18.7)	13 (81.2)	16 (100)	
Clinical stage grouping				
II (111)	31 (27.9)	65 (58.6)	96 (86.5)	
III (89)	21 (23.6)	60 (67.4)	81 (91.0)	

Abbreviations: ER=estrogen receptor, HER2=human epidermal growth factor receptor-2, neg=negative, pos=positive, pCR= pathologic complete response,PR=progesterone receptor

Table 4 Additional treatment

	Conventional Dose <i>N</i> (%)	Dose Dense <i>N</i> (%)	Total <i>N</i> (%)
Pre-treatment determination by breast surgeon of surgery required if neoadjuvant therapy not given			
breast conservation	9 (8.9)	10 (10.1)	19 (9.5)
mastectomy	90 (89.1)	75 (75.8)	165 (82.5)
unknown	2 (2.0)	14 (14.1)	16 (8.0)
Surgery performed after neoadjuvant therapy			
Breast conservation	56 (55.4)	41 (41.4)	97(48.5)
Mastectomy	45 (44.6)	58 (57.4)	103(51.5)
Post-operative radiation therapy			
No	0 (0)	2 (2.0)	2 (1.0)
Yes	101 (100)	97 (98.0)	198 (99.0)
Adjuvant endocrine therapy			
none	32 (31.7)	34 (34.3)	66 (33.0)
Tamoxifen alone	18 (17.8)	26 (26.3)	44 (22.0)
AI alone	5 (5.0)	0 (0)	5 (2.5)
Tamoxifen + LH-RH agonist	11 (10.9)	8 (8.1)	19 (9.5)
LH-RH agonist alone	1 (1.0)	2 (2.0)	3 (1.5)
Sequential tamoxifen/AI	34 (33.7)	27 (27.3)	61 (30.5)
AI +LH-RH agonist with or without previous tamoxifen	0 (0)	2 (2.0)	2 (2.0)
Trastuzumab therapy			
no	86 (85.1%)	61 (61.6%)	147(73.5%)
yes	15 (14.9%)	38 (38.4%)	53 (26.5%)

Abbreviations: AI=aromatase inhibitor, LH-RH=luteinizing hormone releasing hormone

Table 5 Toxicity of neoadjuvant chemotherapy

	Conventional Dose N(%)	Dose Dense N(%)	Total N(%)
No. of patients	101 (50.5)	99 (49.5)	200(100)
Grade III-IV toxicities			
Neutropenia	63 (62.4)	7 (7.1)	70 (35.0)
Neutropenic fever	16 (15.8)	10 (10.1)	26 (13.0)
Myalgias	8 (7.9)	2 (2.0)	10 (5.0)
Neuropathy	8 (7.9)	3 (3.0)	11 (5.5)
Asthenia	8 (7.9)	12 (12.1)	20 (10.0)
Dose delays/reductions/deletions	36(35.6)	40 (40.4)	76 (38.0)

Table 6 Second malignancies

	Conventional dose N(%)	Dose dense N(%)	Total N(%)
No. of patients	101 (50.5)	99 (49.5)	200(100)
Ipsilateral bc	1(1.0)	1(1.0)	2(1.0)
Contralateral bc	6 (5.9)	6 (5.9)	10(5.0)
Other malignancy *	5 (5.0)	5 (5.1)	10(5.0)

Abbreviations: bc=breast cancer, No.=number. *colon cancer (2), renal cell carcinoma (1), melanoma (1), ovarian cancer (1), uterine cancer (2), Chronic lymphocytic leukemia (1), angiosarcoma (2) chondrosarcoma (1). (Total of 11 “other” malignancies: 1 patient had both uterine cancer and angiosarcoma)

Table 7 “Real-World” reports of AC-paclitaxel neoadjuvant chemotherapy

Ref, Country	Years of study	n	HER2pos/HER2neg HRpos/ triple negative/ unknown #	% of patients who received anthra- cycline + taxane based NAC	Median follow- up	pCR	Survival	% of patients who underwent breast conserving surgery
Population-based registry based study								
LeVassuer N et al (13) Canada	2005- 2010	267	34/43/21/2	60 %	7.4 yrs	28%	5-yr OS; pPCR- 88% Non- pCR- 73%	NR
1-2 institution retrospective cohort studies								
Papazisis KT et al (14) Greece	2008- 2018	203	38//39/23/0	"most"	1.7 yrs	42%	Median DFS: pCR -not reached No pCR- 7.58 yrs	NR
Choi M et al (15) Korea	2004- 2013	353	28/54*/30/0	100%	36.5 months	24%	5 yr OS 84.8 %	NR
Krishnan Y et al (16) Kuwait	1998- 2009	365	28/44/21/6	83%	Not reported	14%	Median DFS-104 mo 5 yr OS 67%	19%
Cabrera-Galeana (17) Mexico	2007- 2015	2216	26/52/22/0	NR	60.7 months	33%	5 yr OS 86%	NR
Matteo Luca Battisti N et al (18) United Kingdom	2013- 2017	789	38/36/26/0	92 %- anthracycline 98%-taxane	22.4 months	33%	Median DFS- pCR- 188.6 mo Median DFS-no pCR- 83.8 mo	NR
Current study, Israel	2003- 2012	200	33/53/15/0	100%	9.5 years	26%	10- year OS -70% 5 yr OS 85%	48.5

Abbreviations: AC=doxorubicin+cyclophosphamide Ref=reference,HR=hormone receptor(Estrogen receptor/progesterone receptor).
PCR=pathologic complete response, OS=Overall survival, DFS=disease free survival, NR=not reported, NAC=neoadjuvant
chemotherapy, conserv=conservation , n= number of patients in report

percentages are rounded to nearest whole number*includes patients with HER2pos HR pos tumors.

Figures

Figure 1

Survival Curves for all 200 patients

- a Distant disease- free survival
- b Event-free survival
- c Overall survival

Figure 2

Survival curves by treatment regimen (standard vs dose-dense)

a Event-free survival

b Overall survival

Figure 3

Survival curve by tumor subtype (HR pos/HER2neg, HER2 pos, Triple neg)

a Event-free survival

b Overall survival

Figure 4

Survival by pCR for all 200 patients

a Event-free survival

b Overall survival

Figure 5

Survival according to pCR, HER2pos patients (N=65)

a Event-free survival

b Overall survival