COMPARATIVE STUDY OF NEOADJUVANT CHEMOTHERAPY VS CHEMO-ENDOCRINE THERAPY IN HORMONE RECEPTOR POSITIVE, HER.2 NEGATIVE BREAST CANCER

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ABSTRACT:

Background: Neoadjuvant chemotherapy (NACT) has become a standard treatment for patients with locally advanced, high grade, HER2-positive, and TNBC. Hormone receptor-positive/HER2-negative breast cancer sensitivity to NACT is low, with lower pCR rates. Neoadjuvant chemo-endocrine therapy may become a new strategy to improve pCR in HR-positive/HER2-negative patients. We conducted a randomized trial to assess efficacy of neoadjuvant chemo-endocrine therapy vs chemotherapy in hormone positive, HER.2 negative breast cancer.

Method: premenopausal females with stage II-III, ER-positive, HER.2-negative, invasive breast cancer (n: 152) were randomly assigned (1:1) to received neoadjuvant chemotherapy or chemo-endocrine therapy. The primary objective was pCR. The secondary objectives included tumor downstaging to conservative breast surgery, adverse events, and DFS.

Results: there was significant increase in frequency of complete, marked and partial pathological response in chemo-hormonal group ***(p <0.001)***, significant reduction of radiological LN(s) size in chemo-hormonal group ***(P =0.046),*** a significant reduction of ki67 level after treatment in both groups ***(p <0.001)***, a more significant reduction was in chemo-hormonal group ***(P =0.022).*** Event free survival (EFS) estimates 94.7% at 20 months interval and 82.7% at 40 months interval in chemotherapy group, also EFS estimates 97.1% at 20 months interval and 92.8 % at 40 months interval in chemo-hormonal group with near significant difference between 2 groups ***(P =0.074).*** No significant difference in OS at 20 and 40 months between both groups ***(P =0.163).***

Conclusions: neoadjuvant chemo-endocrine therapy significantly improves pCR, radiologic tumor downstaging, decrease ki67, and EFS compared with chemotherapy in HR-positive, HER2-negative breast cancer.

Keywords: breast cancer, neoadjuvant chemotherapy, chemo-endocrine therapy, estrogen receptor positive, pathologic complete respone

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INTRODUCTION

Neoadjuvant systemic therapy (NAST) has become widely used in breast cancer as it promotes tumor downstaging ***(Generali et al., 2018)***. Neoadjuvant chemotherapy (NACT) has become a standard treatment for patients with locally advanced, high grade tumors, HER2-positive, and triple negative breast cancer (TNBC), it significantly improves the pathological complete response (pCR) ***(Loibl et al., 2021)***. Hormone receptor-positive/HER2-negative breast cancer sensitivity to NACT is low, with lower pCR rates ***(Cortazar et al., 2014)***. Neoadjuvant endocrine therapy (NET) is generally considered to be a suitable option for HR-positive patients unfit for chemotherapy or surgery ***(Charehbili et al., 2014)***. Neoadjuvant chemo-endocrine therapy (NCET) may become a new treatment strategy to improve pCR in HR-positive/HER2-negative patients and further improve their survival ***(Li et al., 2023)***.

PATIENT AND METHOD

Study Design and Patients

The current study was randomized controlled phase II open label trial. The eligibility criteria included Estrogen receptor-positive and HER2-negative breast cancer patients, with histological stage of IIa-IIIc, premenopausal patients, ECOG scores of 0-2 points, measurable and evaluable breast tumor pathologically confirmed as invasive mammary carcinoma, patients didn't receive previous chemotherapy or endocrine therapy, normal or acceptable kidney, liver, cardiovascular, and bone marrow functions. Exclusion criteria included pregnant women or nursing mothers, distant metastasis, a history of malignant tumor or

complicated with other malignant tumors in addition to breast cancer, mental illness or other conditions affecting the patient compliance, other serious diseases or medical conditions, uncontrolled acute infection, and allergic constitution and any known or suspected drug allergy. All patients provided written informed consent. This study was approved by the Institutional Review Board of Mansoura Faculty of Medicine, Mansoura University.

Histopathology and scoring of biomarkers

ER and PR were initially assessed in the laboratory. ER and PR classified according to the Allred score. In the Allred score, 1–8 is described as receptor positive. HER2 was also assessed in the laboratory. Tumors were considered as over-expressing if they scored 3+ during immune-histochemistry using the Dako HercepTest II Kit or if they show greater than two-fold amplification of the HER2 gene as assessed by fluorescent in situ hybridization using the Her-2 FISH: PathVysion HER-2 DNA probe kit. Fluorescent in situ hybridization (FISH) testing will be only carried out for tumors that scored 2+ during immune-histochemistry. The tumors that score 0–1+ during immune-histochemistry or FISH (−) were eligible for this report. KI67 proliferation index was assessed for all cases before and after treatment.

Treatment

Eligible patients were randomly assigned in a 1:1 ratio to either receive neoadjuvant chemotherapy (doxorubicin 60mg/m2 IV and cyclophosphamide 600mg/m2 IV on day 1 every 3 weeks for 4 cycles) followed by (docetaxel 75mg/m2 IV on day 1 every 3 weeks for 4 cycles) plus letrozole with goserelin depending on hormonal status *(experimental arm)* , or to receive neoadjuvant chemotherapy (doxorubicin 60mg/m2 IV and cyclophosphamide 600mg/m2 IV on day 1 every 3 weeks for 4 cycles) followed by (docetaxel 75mg/m2 IV on day 1 every 3 weeks for 4 cycles) *(active comparator arm).* After whole neoadjuvant treatment regimen was recieved in each arm, patients underwent surgery either breast conservative surgery or modified radical mastectomy and pathological response was assessed according to Miller-payne criteria. All 152 Patients received adjuvant therapy; as aromatase inhibitors (AIs) plus zoladex, or tamoxifen plus zoladex, or tamoxifen, or AIs after oophrectomy.149 patients received postoperative radiotherapy (PORT) and 3 patients did not receive PORT as they lost follow up after surgery. Adverse events and laboratory abnormalities were assessed according to Common Terminology Criteria for Adverse Events (CTCAE) v5.0. Patients were followed for two years by clinical examination every three months and mammogram once a year and other radiological and laboratory investigations according to results of clinical examination.

Statistical analysis

The primary objective was to compare pCR rates after neoadjuvant chemotherapy and chemo-endocrine therapy in hormone positive, HER.2 negative breast cancer. The secondary objectives were tumor downstaging to conservative breast surgery, adverse events, and disease free survival (DFS). Statistical analysis was done using SPSS. All statistical tests were two-sided, and P values < 0.05 were considered significant.

RESULTS

Patient baseline characteristics

The study conducted from January 2020 to May 2023. A total of 152 patients were randomly assigned to 2 groups in a ratio of 1:1 (76 patients in the neoadjuvant chemo-endocrine group and 76 patients in the chemotherapy group). All enrolled patients completed all planned cycles of allocated treatment. Patient's demographics and tumor clinico-pathological characteristics were well balanced between the 2 study groups. ER, PR and HER2 were positive in 100.0%, 92.1% and 0.0% respectively, HER2 was assessed by IHC in all patients, for patients with HER2 scoring +2 or +3, further evaluation by fluorescent in situ hybridization (FISH) was performed to confirm HER2 negativity. Progesterone receptor positivity was more frequent in chemo-hormonal group compared to chemotherapy group. All cases were ER-positive, HER.2-negative (Table 1).

Table 1: patient's demographics and tumor clinico-pathological characteristics among studied groups

Parameter		Chemotherapy group (N=76)	Chemo-hormonal group (N=76)	P-value
Age	**Mean ± SD**	**43.8 ± 8.41**	**43.18 ± 8.05**	0.602
Presence of clinical skin infiltration	**Count (%)**	**35 (46.1%)**	**39 (51.3%)**	0.516
Affected nipple and areola	**Count (%)**	**24 (31.6%)**	**32 (42.1%)**	0.179
Clinical mass size*	**Median (Min-Max)**	**3.0 (1.6-10.0)**	**3.0 (1.0-6.0)**	0.053
Clinical LN	**Not palpable**	**14 (18.4%)**	**11 (14.5%)**	0.512
	Palpable	**62 (81.6%)**	**65 (85.5%)**	
Trucut tumor type	**IDC**	**51 (67.1%)**	**48 (63.2%)**	0.703
	ILC	**5 (6.6%)**	**4 (5.3%)**	
	IDC with CIS	**20 (26.3%)**	**23 (30.3%)**	
	ILC with CIS	**0 (0.0%)**	**1 (1.3%)**	
Trucut grade	**Grade I**	**0 (0.0%)**	**1 (1.3%)**	0.321
	Grade II	**56 (73.7%)**	**61 (80.3%)**	
	Grade III	**20 (26.3%)**	**14 (18.4%)**	
Estrogen receptor	**Negative**	**0 (0.0%)**	**0 (0.0%)**	
	Positive	**76 (100.0%)**	**76 (100.0%)**	
Estrogen receptor positivity**	**Mean ± SD**	**7.28 ± 1.37**	**7.11 ± 1.63**	0.485
progesterone receptor	**Negative**	**12 (15.8%)**	**0 (0.0%)**	**<0.001**
	Positive	**64 (84.2%)**	**76 (100.0%)**	
Progesterone receptor positivity**	**Mean ± SD**	**5.56 ± 2.83**	**6.42 ± 1.76**	**0.027**
HER2 receptor	**Negative**	**76 (100.0%)**	**76 (100.0%)**	
	Positive	**0 (0.0%)**	**0 (0.0%)**	
HER2 receptor by IHC	**Negative**	**19 (25.0%)**	**41 (53.9%)**	**<0.001**
	+1	**13 (17.1%)**	**17 (22.4%)**	
	+2	**18 (23.7%)**	**15 (19.7%)**	
	+3	**26 (34.2%)**	**3 (3.9%)**	

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, IDC with CIS: invasive ductal carcinoma with carcinoma in situ, ILC: invasive lobular carcinoma with carcinoma in situ, N: number, DCIS: ductal carcinoma in situ, SD: standard deviation, HER2: human epidermal growth factor receptor2, IHC: immune-histochemistry
Continuous variables are expressed as median (min-max)*. Data are compared Mann-whitney tests* or mean ± SD**. SD, standard deviation Data are compared using independent T test**. Chi square test (Fisher;'s Exact test) for comparison of categorical parameters. **P** between both groups.
**significant (P value < 0.05)

Primary objective: pathologic complete response (pCR)

There was significant increase in frequency of complete, marked and partial pathological response in chemo-hormonal group compared with chemotherapy group ***(P <0.001).*** Non-responders were significantly more among chemotherapy group. (Table 2)

Table 2: Comparison of pathological response among studied groups

Parameter		Chemotherapy group (N=76)	Chemo-hormonal group (N=76)	P-value
Pathological response	**Complete pathological response**	**8 (10.5%)**	**12 (15.8%)**	**<0.001**
	Marked pathological response	**5 (6.6%)**	**20 (26.3%)**	
	Partial pathological response	**34 (44.7%)**	**38 (50.0%)**	
	Minimal pathological response	**9 (11.8%)**	**4 (5.3%)**	
	No response	**20 (26.3%)**	**2 (2.6%)**	

N: number, Chi square test for comparison of categorical parameters. **P** between both groups.
**significant (P value < 0.05)

Secondary objectives: tumor down staging to conservative breast surgery, adverse events, and disease free survival (DFS).

Radiologic evaluation of patients after treatment revealed significant reduction of radiological LN size in patients received neoadjuvant chemo-hormonal therapy compared to patients received neoadjuvant chemotherapy alone (***P* =0.046)**. Additionally, radiological tumor size, radiological LN, radiological LN size were significantly decreased in both groups before and after therapy, also radiological staging underwent significant downstaging in both groups before and after therapy. All enrolled cases underwent surgical resection, 56% underwent modified radicl

mastectomy (MRM) and the rest underwent CBS with no significant difference between both groups. Gross residual tumor presented in 125 cases (82.2%). There was significant decrease in frequency of lymphovascular invasion and comedo necrosis in the postoperative specimen among chemo-hormonal group compared with chemotherapy group. Otherwise no other significant difference could be detected. Lymph node characteristics were illustrated in (Table 3).

Table 3: Comparison of type of surgery and histological characteristics after surgery among studied groups

Parameter		Chemotherapy group (N=76)	Chemo-hormonal group (N=76)	P-value
Type of surgery	MRM	45 (59.2%)	41 (53.9%)	0.513
	CBS	31 (40.8%)	35 (46.1%)	
Presence of gross residual tumor		61 (80.2%)	64 (84.2%)	0.415
Size of residual tumor*	Median (Min-Max)	2.0 (1.0-7.0)	2.0 (1.0-6.0)	0.952
Histological diagnosis	No residual	15 (19.7%)	12 (15.8%)	0.775
	IDC	58 (76.3%)	60 (78.9%)	
	ILC	3 (3.9%)	4 (5.3%)	
Grade of residual invasive carcinoma (N=125)	I	2 (3.3%)	5 (7.8%)	0.155
	II	51 (83.6%)	56 (87.5%)	
	III	8 (13.1%)	3 (4.7%)	
Size of largest carcinoma*	Median (Min-Max)	2.0 (1.0-7.0)	2.0 (0.5-6.0)	0.600
Residual tumor cellularity*	Median (Min-Max)	60.0 (5.0-95.0)	50.0 (5.0-90.0)	0.058
Presence of lymphovascular invasion (N=125)		47 (77.0%)	38 (59.4%)	**0.034**
Presence of necrosis		17 (22.4%)	16 (21.1%)	0.844
Type of necrosis	Focal	13 (76.5%)	16 (100.0%)	**0.038**
	Comedo	4 (23.5%)	0 (0.0%)	
Sentinel LN*	Median (Min-Max)	3.0 (1.0-6.0)	3.0 (1.0-8.0)	0.381
Total axillary LN*	Median (Min-Max)	12.0 (1.0-39.0)	11.5 (1.0-37.0)	0.940
N of LN with macromets*	Median (Min-Max)	1.50 (0-15)	1.0 (0-14)	0.156
Size of largest met lN	Median (Min-Max)	1.0 (1-2)	1.0 (1-2)	0.519
N of LN with micromets*	Median (Min-Max)	0 (0-1)	0 (0-3)	0.485
N of LN with iso tumor cells*	Median (Min-Max)	2.0 (0-15)	1.0 (0-14)	0.318
N of LN with no tumor cells *	Median (Min-Max)	8.0 (0-39)	9.0 (0-31)	0.556
Presence of extracapsular extension		32 (42.1%)	26 (34.2%)	0.316

MRM: modified radical mastectomy, CBS: conservative breast surgery, Min: minimum, Max: maximum, IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, N: number, DCIS: ductal carcinoma in situ, LN: lymph node(s), macromets: macrometastasis, micromets: micrometastasis, mets: metastasis, iso: isolated
Continuous variables are expressed as median (min-max)*. Data are compared Mann-whitney tests* or mean ± SD**. SD, standard deviation Data are compared using independent T test**. Chi square test (Fisher;'s Exact test) for comparison of categorical parameters. **P** between both groups.
**significant (P value < 0.05).

The comparison of Ki67 before and after neoadjuvant therapy among both studied groups reported a significant decrease in postoperative Ki67 in patients received neoadjuvant chemo-hormonal therapy compared to patients received neoadjuvant chemotherapy alone with **(*P* =0.022).** Additionally, ki67 was significantly decreased in both groups before and after neoadjuvant therapy (***P* <0.001)** as shown in (Figure 1).

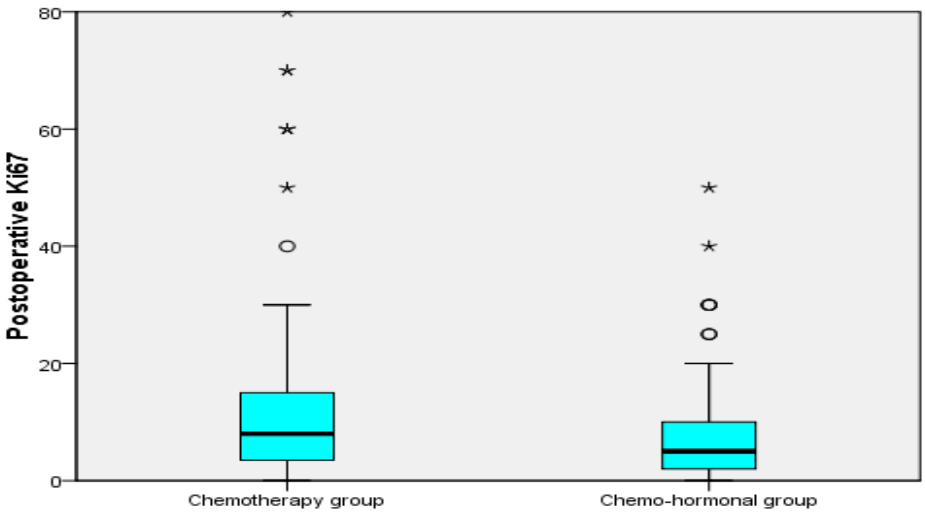

Figure 1: Ki67 in both studied groups

Safety profile and adverse events

The analysis of treatment related adverse events revealed that all neoadjuvant treatments were well tolerated. Musculoskeletal symptoms were most frequent in 46.1% of cases, followed by vasomotor symptoms in 23.7% of cases with no significant difference between both groups. Vasomotor symptoms were more frequent in chemotherapy group with near statistical significance ***(P=0.056).*** Hematological toxicity was reported in 15.1% of cases (grade I & II) mostly in the form of neutropenia and leukopenia and was well tolerated with no significant difference between both groups. There were two disease-related deaths reported in the chemotherapy group due to disease recurrence after surgery.

Survival analysis

The survival analysis revealed that event free survival (EFS) estimates 94.7% at 20 months interval and 82.7% at 40 months interval in chemotherapy group, also EFS estimates 97.1% at 20 months interval and 92.8 % at 40 months interval in chemo-hormonal group with near significant difference between 2 groups ***(P =0.074)*** (figure 2).

overall survival (OS) estimates 97.2% at 20 months interval and 97.2% at 40 months interval in chemotherapy group, also OS estimates 100 % at 20 months interval and 40 months interval in chemo-hormonal group with no significant difference between 2 groups ***(P =0.163)*** (figure 2).

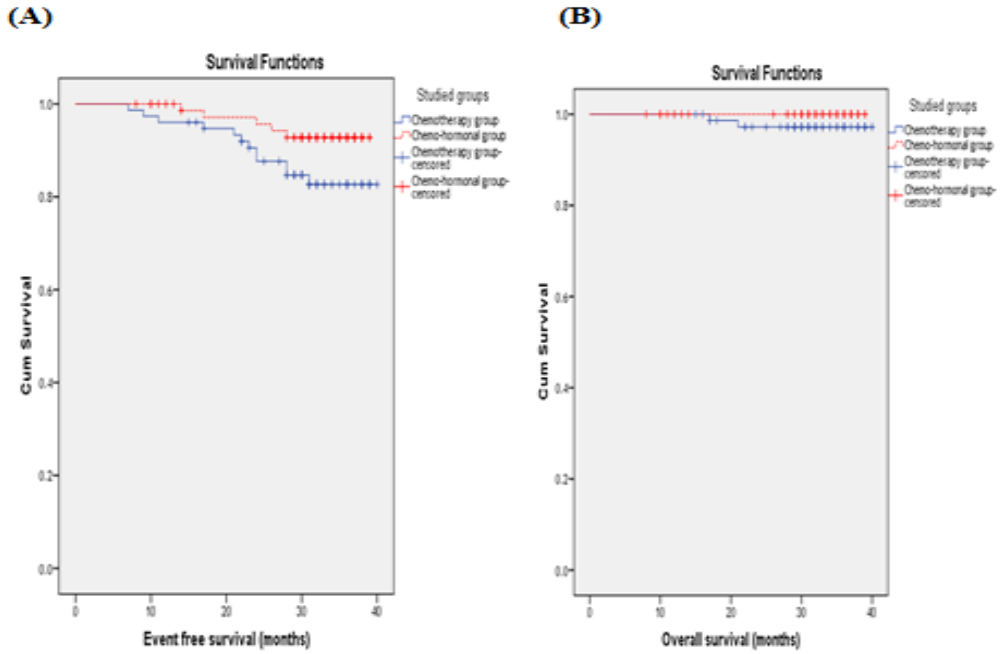

Figure 2: (A) Event free survival (EFS) and (B) overall survival (OS) as regard studied groups

DISCUSSION

This study started in January 2020, on newly diagnosed hormone positive, HER.2 negative premenopausal breast cancer patients in Oncology Center, Mansoura University. One hundred fifty two cases with newly diagnosed stage II and III hormone positive, HER.2 negative breast cancer were randomized allocated at a 1:1 ratio into two arms, (*experimental arm*); patients received neoadjuvant concurrent chemo-hormonal therapy and (*active comparator arm*); patients received neoadjuvant chemotherapy only.

There was no significant difference between the two study arms as regard patient's baseline characteristics and clinico-pathological characteristics.

Fifty-three percent of enrolled cases in this study were clinically diagnosed as stage III without significant difference between study groups, this percentage is more than the percentage of cases enrolled in CBCSG-036 trial ***(Yu et al., 2019)*** and diagnosed as clinical stage III (42%), while this percentage is much less than the percentage of cases diagnosed as stage III breast cancer (90.3%) and enrolled in phase III trial by ***(Mohammadianpanah et al., 2012)***, which was designed as a study on locally advanced breast cancer.

On baseline radiologic evaluation of cases enrolled in this study, 82.9% of cases had detected suspicious axillary LN(s), 51.3% of cases were diagnosed as stage II and the rest were stage III in radiological staging. After neoadjuvant treatment, there was significant reduction of radiological LN(s) size in patients received chemo-hormonal therapy compared to patients received chemotherapy alone with ***(P =0.046)*.**

Additionally, radiological tumor size, radiological LN, and radiological LN size were significantly decreased in both study groups before and after therapy. Radiological staging underwent significant downstaging in both groups before and after neoadjuvant therapy, which is in agreement with the data from NACED trial that showed significant reduction in tumor size and tumor downstaging after neoadjuvant concurrent chemo-endocrine therapy with (***P* =0.035)*(Sugiu et al., 2015)*** and ***(Mohammadianpanah et al., 2012)*** studies.

CBCSG-036, a multicenter trial, stated that there was significant improve in clinical response rates in chemo-endocrine group ***(P =0.033)*** compared to chemotherapy group, which was more prominent in tumors with higher ki67 (more than 20%).***(Yu et al., 2019)***.

As regard type of surgery, fifty six percent of cases underwent modified radicl mastectomy (MRM) with no significant difference between both groups which could be owed to the achievement of radiologic complete response and the absence of clip in some cases, and due to surgical issues, which is in co-ordinance with the data from NACED trial that showed similar results ***(Sugiu et al., 2015)***.

On the other hand, a single-arm study of concurrent neoadjuvant chemo-endocrine therapy for postmenopausal females revealed high percentage of conservative breast surgery (CBS) (96.2%) ***(Watanabe et al., 2010)***, another study on luminal B-like,HER2-negative breast cancer showed increased percentage of CBS (67%) in patients received neoadjuvant treatment with no significant difference between NCT and NCET groups ***(Matsunuma et al., 2020)***.

The median level of ki67 before neoadjuvant treatment was 30, which considered high, and showed significant reduction after neoadjuvant treatment in both groups ***(P =<0.001)***, and a more significant reduction of postoperative ki67 level in chemo-hormonal group ***(P =0.022)***, which is in agreement with data from NACED trial ***(Sugiu et al., 2015)***, CBCSG-036 trial ***(Yu et al., 2019)***, and a trial performed on luminal B- like, HER2-negative breast cancer ***(Matsunuma et al., 2020)***, they all showed a significant reduction in postoperative ki67 level in chemo-hormonal group compared with chemotherapy group.

There was significant increase in frequency of complete, marked and partial pathological response in chemo-hormonal group ***(P <0.001)***. Non-responders were significantly more among chemotherapy group, that is in co-ordinance with data from a phase III study on locally advanced breast cancer in postmenopausal females that showed a significant higher pCR in chemo-hormonal group ***(P =0.040) (Mohammadianpanah et al., 2012)***.

On the other hand, NACED-phase II trial showed that there was no significant difference in pCR rates between chemo-endocrine and chemotherapy groups ***(P* =1.000) *(Sugiu et al., 2015)*** and ***(Matsunuma et al., 2020)*** studies. The different results can be owed to the relative smaller number of cases enrolled in these studies.

A meta-analysis of 5 randomized controlled trials was conducted, these trials included (N: 566). Neoadjuvant chemo-hormonal therapy didn't significantly improve pCR rates (OR 1.35, 95% CI 0.77–2.38, ***P* =0.30**) in HR-positive breast cancer. ***(Li et al., 2023)***.

The analysis of treatment related adverse events revealed that all neoadjuvant treatments were well tolerated. Musculoskeletal symptoms were most frequent in 46.1% of cases, followed by vasomotor symptoms in 23.7% of cases with no significant difference between both groups, in co-ordinance with adverse events reported in a phase III on locally advanced breast cancer in postmenopausal females.***(Mohammadianpanah et al., 2012)***.

There were two disease-related deaths reported in the chemotherapy group due to disease recurrence after surgery unlike the trial performed on luminal

B- like, HER2-negative breast cancer that reported one treatment related death in each group.***(Matsunuma et al., 2020)***.

The survival analysis revealed that event free survival (EFS) estimates 94.7% at 20 months interval and 82.7% at 40 months interval in chemotherapy group, also EFS estimates 97.1% at 20 months interval and 92.8 % at 40 months interval in chemo-hormonal group with near significant difference between 2 groups ***(P =0.074).***

On the other hand, CBCSG-036 trial reported that no significant difference in progression-free survival (PFS) between the 2 groups **(*P* = .188**), but cases with a higher baseline Ki67 level appeared to get a greater PFS benefit from NCET (2-year PFS rate of 91.5% in the NCET group vs 76.5% in the NCT group**; *P* = .058**).***(Yu et al., 2019)***.

OS estimates 97.2% at 20 months interval and 97.2% at 40 months interval in chemotherapy group, also OS estimates 100 % at 20 months interval and 40 months interval in chemo-hormonal group with no significant difference between 2 groups ***(P =0.163).***

Unlike, SHPD002 phase III trial which stated that concurrent chemo-endocrine therapy significantly improved survival outcome in premenopausal patients Improved DFS (log-rank ***P =0.001***) and OS (log-rank ***P =0.003***). (3-year OS, 100% with GnRHas, vs 88.2% without; log-rank ***P =0.034***) ***(Zhou et al., 2022)***, as this study was performed on 236 cases with locally advanced breast cancer.

Conclusions:

The data from current study revealed that chemo-endocrine therapy significantly improves pCR, radiologic tumor downstaging, decrease ki67 level, and EFS compared with chemotherapy in neoadjuvant treatment of HR-positive, HER2-negative breast cancer.

Based on our findings, we recommend further studies to evaluate efficacy and safety of concurrent neoadjuvant chemo-endocrine therapy vs chemotherapy in hormone-positive, HER.2-negative breast cancer patients with a longer follow up period for better assessment of survival analysis.

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