ORIGINAL RESEARCH

EFFICACY OF PEGYLATED LIPOSOMAL DOXORUBICIN-BASED NEOADJUVANT CHEMOTHERAPY IN BREAST CANCER: A SINGLE CENTER EXPERIENCE

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ABSTRACT

Purpose: Neoadjuvant chemotherapy using a doxorubicin-based regimen has recently become a common therapeutic option for operable breast cancer. This study aimed to investigate the efficacy of polyethylene glycol-coated liposomal doxorubicin (PLD)-based chemotherapy for breast cancer in neoadjuvant settings.

Methods: A total of 227 female operable breast cancer patients who were diagnosed between January 2009 and December 2017 and completed neoadjuvant PLD-based chemotherapy were retrospectively included. The logistic regression analysis was used to determine the associations between pathologic complete response (pCR) and preoperative clinicopathological characteristics. The breast cancer recurrence rate was estimated using the survival analysis.

Results: A higher pCR rate was found in the patients with clinically negative lymph nodes and HER2-enriched patients. Moreover, the patients who achieved pCR also had a better prognosis outcome. A recurrence rate of 11.5% (n=26) was observed during a median follow-up of 11.63 months, and the recurrence rate of the pCR group (2.04%; 95% CI = 0.29-13.62) was lower than the non-pCR group (14.62%; 95% CI = 10.12-20.87). Higher histological grade was also associated high pCR rate (52.0% vs 40.0%).

Conclusion: The use of PLD-containing chemotherapeutics in neoadjuvant settings might have benefits for non-metastatic operable breast cancer in Taiwanese females.

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INTRODUCTION

Chemotherapy has always been considered the standard treatment option for invasive breast cancer. Previously, chemotherapy played a role only in adjuvant settings [1,2]. More recently, the combined chemotherapy approach was introduced in neoadjuvant settings, and showed benefits in prognosis outcome for operable breast cancer [3-5]. Neoadjuvant chemotherapy is given to eliminate invasive tumors, axillary lymph nodes and occult distant metastases, or to reduce an invasive lesion before breast cancer surgery. Pathologic complete response (pCR) is a term used to describe a patient who has achieved a complete response that fully reflects the chemosensitivity in an invasive or occult distant metastatic site following complete neoadjuvant chemotherapy. Patients who have achieved pCR are more likely to have a better prognostic outcome [6,7].

Doxorubicin, in a polyethylene glycol-coated and liposome-encapsulated form (PEGylated liposomal doxorubicin; PLD), is an effective chemotherapeutic option that can be used in place of an anthracyclines-based regimen [8,9]. The PLD exhibits a stronger ability to penetrate the tumor and has a longer circulation time, which could increase tumor exposure to the drug and improve the treatment efficacy [10]. Cardiac dysfunction induced by chemotherapeutics is an important issue that warrants more attention in breast cancer chemotherapy. The PLD generally shows a lower cardiotoxicity profile in comparison with conventional doxorubicin or a conventional anthracycline-based regimen [11-13].

The PLD has been shown to have a promising therapeutic and safety toxic profile when used to treat breast cancer in both adjuvant and neoadjuvant settings [14-

16]. However, there is insufficient data on the efficacy of PLD in neoadjuvant settings in Taiwan's breast cancer population. This study aimed to investigate the treatment efficacy of operable breast cancer patients with neoadjuvant PLD-containing chemotherapeutics, to demonstrate the predictors of pCR and to identify patient populations who would benefit from neoadjuvant chemotherapy.

METHODS

Dataset

The dataset was obtained from the Taichung Veterans General Hospital Research Database under an Institutional Review Board-approved protocol (IRB number: CE19104B). The study cohort included 227 female breast cancer patients who were diagnosed between January 2009 and December 2017 and who received PLD-based neoadjuvant chemotherapy before initial surgical treatment. Breast cancer patients with clinical preoperative stage I to III cancer characterized as lymph node positive, inflammatory, of greater tumor size and/or with small tumors in females with small breasts (which may not achieve negative margins) were treated with neoadjuvant chemotherapy. Neoadjuvant chemotherapy was used not only to cure disease and improve breast conservation but also to gain information about efficacy. Clinical preoperative stage IV patients, especially those characterized with inflammatory, larger tumor size and unachievable negative margins, were usually given neoadjuvant chemotherapy as a palliative treatment. All patients had received surgical treatment for invasive breast cancer and were regularly followed up. As mentioned in the clinical standard of care procedures, other therapies including targeted, hormone and radiation therapy, were given after the initial neoadjuvant treatment.

Each patient was included retrospectively into the database and observed longitudinally. The dataset contained data on age at diagnosis, preoperative stage, neoadjuvant chemotherapy response, pathology reports, surgery method, treatment history and survival information. Patients received PLD as a 90-minute infusion of 35–40 mg/m² every 21 days for four cycles. The PLD-based regimens included the following: four cycles of 5-fluorouracil (500 mg/m²), PLD and cyclophosphamide (500 mg/m²); four cycles of PLD and cyclophosphamide (500 mg/m²) followed by 12 cycles of weekly paclitaxel (80 mg/m²) ± carboplatin (2 AUC); or four cycles of PLD and cyclophosphamide (500 mg/m²) followed by four cycles of docetaxel (75 mg/m²) and/or carboplatin (6 AUC). Patients with HER2-enriched subtype received trastuzumab and/or pertuzumab concurrently with taxane.

In the stage IV patients, single metastatic lesions in the

pre-operative image that were subsequently shown to be stable or regressive change after complete neoadjuvant chemotherapy were considered to be operable breast cancer. All patients with lymph node stage 3 (N3) lesions were diagnosed by fine needle aspiration of the metastatic lymph node.

The neoadjuvant chemotherapy response was based on local histopathologic assessments. The pCR in this study was defined according to the MD Anderson Cancer Center and Neo-Breast International Group, which means no invasive or noninvasive breast residual, and no invasive residual in nodes (ypT0/is ypN0) [17,18]. Breast cancer recurrence was considered to be a prognostic relevant outcome. Each patient was observed at three months to six months, which involved ultrasound measurements and assessments performed according to clinical guidelines. Patients with histologically confirmed local, regional, or distant metastasis were defined as having recurrence. The follow-up interval was calculated from the date of breast cancer mastectomy until the end of follow-up or the last estimated date of recurrence recorded in the database.

Statistical analysis

The baseline characteristics of patients are shown as mean, standard deviation, frequency, and percentage in Table 1. The distribution of baseline characteristics according to the neoadjuvant chemotherapy response—pathologic complete response (pCR) vs. non-pathologic complete response (non-pCR)—was estimated using chi-squared or Fisher's exact test for categorical variables and was estimated using two-sample t-test for continuous variables. Logistic regression analysis was performed to determine which characteristics were significantly correlated with pCR. Univariate and multivariate Cox proportional hazard regression analyses were used to determine the association between breast cancer recurrence and baseline characteristics. The cumulative incidence risk of breast cancer recurrence according to the neoadjuvant chemotherapy response was calculated using Kaplan-Meier failure curves, and the difference between curves was examined by log-rank test. All *p*-values were two-sided and *p*-values less than or equal to 0.05 were considered statistically significant. All analyses were performed using Stata version 14.0 (Stata Statistical Software: Release 14, 2015, StataCorp. TX, USA).

RESULTS

According to the preoperative staging of disease, 58.8% of stage I, 16% of stage II and 15.6% of stage III patients achieved pCR. The results in Table 1 also show the pCR rates based on preoperative clinicopathological factors. Patients with high histological grade, negative PR status

TABLE 1.
PREOPERATIVE CHARACTERISTICS OF BREAST
CANCER PATIENTS ACCORDING TO THE
NEOADJUVANT CHEMOTHERAPY RESPONSE.

Variables	All patients n (%)	pCR n (%) [*]	Non-pCR n (%) [†]	p-value [‡]
Cases [§]	227	50 (22%)	177 (78%)	
Age (year)	49.7 ± 9	49.9 ± 7.6	49.6 ± 9.3	0.866
Histological grade				0.043
1-2	120 (52.9%)	20 (40%)	100 (56.5%)	
3	93 (41%)	26 (52%)	67 (37.9%)	
Unknown	14 (6.2%)	4 (8%)	10 (5.6%)	
ER status				0.297
Negative	68 (30%)	19 (38%)	49 (27.7%)	
Positive	157 (69.2%)	31 (62%)	126 (71.2%)	
Unknown	2 (0.9%)	0 (0%)	2 (1.1%)	
PR status				0.008
Negative	98 (43.2%)	30 (60%)	68 (38.4%)	
Positive	127 (55.9%)	20 (40%)	107 (60.5%)	
Unknown	2 (0.9%)	0 (0%)	2 (1.1%)	
Her2 status				<0.001
Negative	151 (66.5%)	20 (40%)	131 (74%)	
Positive	75 (33%)	30 (60%)	45 (25.4%)	
Unknown	1 (0.4%)	0 (0%)	1 (0.6%)	
Molecular subtype				0.098
Luminal type	163 (71.8%)	31 (62%)	132 (74.6%)	
Her2-enriched	27 (11.9%)	10 (20%)	17 (9.6%)	
TNBC	35 (15.4%)	9 (18%)	26 (14.7%)	
Unknown	2 (0.9%)	0 (0%)	2 (1.1%)	

or positive HER2 status had significantly higher pCR rates. Mean age at diagnosis was 49.9 ± 7.6 years in the pCR group, and 49.6 ± 9.3 years in the non-pCR group.

The associations between preoperative factors and pCR rate, using logistic regression analysis, are presented in Table 2. Both univariate and multivariate analyses indicated that patients with preoperative lymph node metastases (cN1-3) had significantly lower odds of achieving pCR compared with patients with no lymph node metastases (crude odds ratio [COR] = 0.43, 95% confidence interval [CI] = 0.23-0.82, *P* = 0.010; adjusted odd ratio [AOR] = 0.45, 95% CI = 0.24-0.98, *P* = 0.045), and patients with HER2-enriched subtype had significantly higher odds of achieving pCR compared with luminal subtype patients (COR = 2.50, 95% CI = 1.05-6.00, *P* = 0.039; AOR = 2.71, 95% CI = 1.08-6.77, *P* = 0.034). Although patients with histological grade 3 had

Variables	All patients n (%)	pCR n (%) [*]	Non-pCR n (%) [†]	p-value [‡]
Primary tumor size preoperative				0.032
cT1	60 (26.4%)	21 (42%)	39 (22%)	
cT2	135 (59.5%)	22 (44%)	113 (63.8%)	
cT3	20 (8.8%)	4 (8%)	16 (9%)	
cT4	8 (3.5%)	1 (2%)	7 (4%)	
Unknown	4 (1.8%)	2 (4%)	2 (1.1%)	
Regional lymph node preoperative				0.009
cN0	94 (41.4%)	29 (58%)	65 (36.7%)	
cN1-3	112 (57.3%)	21 (42%)	109 (63.3%)	
Unknown	3 (1.3%)	0 (0%)	3 (1.7%)	
Clinical stage preoperative				<0.001
I	24 (15%)	20 (40%)	14 (7.9%)	
II	156 (68.7%)	25 (50%)	131 (74%)	
III	32 (14.1%)	5 (10%)	27 (15.3%)	
IV	2 (0.9%)	0 (0%)	2 (1.1%)	
Unknown	3 (1.3%)	0 (0%)	3 (1.7%)	

Abbreviations: ER, estrogen receptor; HER2, human epidermal growth factor receptor; pCR, pathologic complete response; PR, progesterone receptor

* Column percentage of pCR group.

† Column percentage of non-pCR group.

‡ *P* value was estimated using independent two-sample t-test, chi-squared test, or Fisher's exact test.

§ Row percentage of all patients.

marginally significantly higher odds of achieving pCR in the univariate analysis (COR = 1.94, 95% CI = 1.003-3.75, *P* = 0.049), no significant results were found in the multivariate analysis (AOR = 1.58, 95% CI = 0.77-3.24, *P* = 0.210).

All patients completed planned neoadjuvant PLD-based chemotherapy and surgical treatment (37.0% with breast conserving surgery and 62.6% with total mastectomy). In total, 33.0% of the patients with HER2-positive status received target therapy after PLD-based neoadjuvant treatment. Following the PLD-based neoadjuvant treatment, 62.1% of the patients received radiotherapy, and 68.3% underwent hormone therapy. The postoperative characteristics of all patients are summarized in Table 3.

During a median follow-up of 11.63 months (range,

TABLE 2.
LOGISTIC REGRESSION ANALYSIS FOR NEOADJUVANT CHEMOTHERAPY RESPONSE.

Variables	Comparison	Univariate		Multivariate	
		COR (95% CI)	P	AOR (95% CI)	P
Age	year	1.00 (0.97-1.04)	0.865	1.01 (0.97-1.05)	0.697
Primary tumor size preoperative	cT3-4 vs. cT1-2	0.77 (0.28-2.14)	0.614	1.14 (0.26-5.08)	0.863
Regional lymph node preoperative	N1-3 vs. cN0	0.43 (0.23-0.82)	0.010	0.48 (0.24-0.98)	0.045
Clinical stage preoperative	III-IV vs. I-II	0.56 (0.20-1.52)	0.252	0.61 (0.13-2.82)	0.528
Histological grade	3 vs. 1-2	1.94 (1.003-3.75)	0.049	1.58 (0.77-3.24)	0.21
Molecular subtype	HER2-enriched vs luminal type	2.50 (1.05-6.00)	0.039	2.71 (1.08-6.77)	0.034
Molecular subtype	TNBC vs luminal type	1.47 (0.63-3.46)	0.373	1.12 (0.45-2.82)	0.802

Abbreviations: AOR, adjusted odds ratio; COR, crude odds ratio; HER2, human epidermal growth factor receptor; pCR, pathologic complete response; TNBC, triple negative breast cancer

8 to 38.31 months), recurrence was noted in 26 (11.5%) patients. The 18-month recurrence rate based on the Kaplan-Meier method was 2.04% (95% CI = 0.29-13.62) and 14.62% (95% CI = 10.12-20.87) in pCR and non-pCR subjects, respectively. Figure 1 illustrates the number at risk and breast recurrence incidence curve in both groups at 18 months following PLD-based neoadjuvant treatment. According to the incidence curves, the non-pCR group showed a significantly higher incidence compared with the pCR group (log-rank test, $P = 0.019$) during the 18-months follow-up interval.

TABLE 3.
POSTOPERATIVE CHARACTERISTICS FOLLOWING THE NEOADJUVANT CHEMOTHERAPY.

Variables	All patients
Tumor size (mm)	34 ± 24.7
ALN positive (numbers)	3.7 ± 12.1
Histological type	
Non-IDC	22 (9.7%)
IDC	204 (89.9%)
Unknown histological type	1 (0.4%)
Surgery	
Partial mastectomy	84 (37%)
Total mastectomy	142 (62.6%)
Unknown surgery type	1 (0.4%)
With radiotherapy	141 (62.1%)
With hormone therapy	155 (68.3%)
With targeted therapy	75 (33%)
Recurrence	26 (11.5%)

Abbreviations: ALN, axillary lymph node; IDC, invasive ductal carcinoma

Table 4 depicts the Cox proportional hazard regression analysis results of neoadjuvant treatment effects, age at diagnosis, preoperative factors, molecular subtype, surgery type, targeted therapy, hormone therapy and radiation therapy, on breast cancer recurrence. In both the univariate (crude hazard ratio [CHR] = 0.13, 95% CI = 0.02-0.97, $P = 0.047$) and multivariate (adjusted hazard ratio [AHR] = 0.13, 95% CI = 0.02-0.997, $P = 0.050$) analyses, pCR patients had a significantly lower risk of breast cancer recurrence compared with non-pCR patients. In addition, patients with cN1-3 (CHR = 2.51, 95% CI = 1.01-6.24, $P = 0.049$; AHR = 2.92, 95% CI = 1.02-8.35, $P = 0.045$) and histological grade 3 (CHR = 2.88, 95% CI = 1.23-6.73, $P = 0.015$; AHR = 3.97, 95% CI = 1.38-8.35, $P = 0.011$) had a significantly higher risk of breast cancer recurrence.

FIGURE 1.
KAPLAN-MEIER CURVE USING BREAST CANCER 18-MONTHS RECURRENCE RATE AS A FUNCTION OF TUMOR RESPONSE TO NEOADJUVANT CHEMOTHERAPY.

Abbreviations: pCR, pathologic complete response

TABLE 4.
COX PROPORTIONAL HAZARD REGRESSION ANALYSIS FOR BREAST CANCER RECURRENCE.

Variables	Comparison	Univariate		Multivariate	
		CHR (95% CI)	P	AHR (95% CI)	P
Neoadjuvant chemotherapy response	pCR vs. non-pCR	0.13 (0.02-0.97)	0.047	0.13 (0.02-0.997)	0.050
Age	year	1.03 (0.99-1.08)	0.150	1.02 (0.97-1.06)	0.479
Primary tumor size preoperative	cT3-4 vs. cT1-2	4.17 (1.86-9.38)	0.001	2.94 (0.62-13.92)	0.174
Regional lymph node preoperative	cN1-3 vs. cN0	2.51 (1.01-6.24)	0.049	2.92 (1.02-8.35)	0.045
Clinical stage preoperative	III-IV vs. I-II	3.84 (1.74-8.46)	0.001	1.25 (0.26-5.93)	0.778
Histological type	IDC vs. others	0.57 (0.20-1.65)	0.301	0.27 (0.08-0.95)	0.042
Histological grade	3 vs. 1-2	2.88 (1.23-6.73)	0.015	3.97 (1.38-11.43)	0.011
Molecular subtype	HER2-enriched vs. luminal type	2.09 (0.76-5.76)	0.153	1.69 (0.32-8.88)	0.537
Molecular subtype	TNBC vs. Luminal type	2.08 (0.81-5.38)	0.129	0.94 (0.23-3.93)	0.934
Surgery	Total vs. partial mastectomy	2.04 (0.82-5.08)	0.126	1.23 (0.45-3.35)	0.690
Radiotherapy	With vs. without RT	0.48 (0.22-1.04)	0.062	0.39 (0.11-1.40)	0.148
Target therapy	With vs. without TT	0.85 (0.37-1.95)	0.699	0.33 (0.08-1.36)	0.124
Hormone therapy	With vs. without HT	1.01 (0.44-2.33)	0.978	0.80 (0.32-2.05)	0.648

Abbreviations: AHR, adjusted odds ratio; CHR, crude hazard ratio; HER2, human epidermal growth factor receptor; HT, hormone therapy; IDC, intraductal carcinoma; pCR, pathologic complete response; RT, radiotherapy; TNBC, triple negative breast cancer; TT, target therapy

DISCUSSION

This was a retrospective study to observe the tumor response of operable breast cancer patients with neoadjuvant PLD-containing chemotherapeutics in a Taiwanese population. The PLD is used in breast cancer treatment, and various clinical studies have shown the efficacy and safety of PLD-containing treatments [19-22]. However, the efficacy of PLD-containing chemotherapeutics in neoadjuvant settings is less well known, especially for Taiwanese patients. The results of the present study demonstrated the tumor response in a study population with multiple tumor characteristics, which allowed for assessment of predictors of pCR and of patient populations that would benefit from neoadjuvant chemotherapy.

Patients with the HER2-enriched subtype were more likely to achieve pCR, especially those that received targeted therapeutics [23]. According to our results, all HER2-enriched patients (33.0% of total patients) received targeted therapy regimen, including trastuzumab and/or pertuzumab. While hormone receptor-positive disease has previously been shown to have a decreased response to cytotoxic therapy, in this study, the use of anti-HER2 therapy (including trastuzumab or pertuzumab) showed a similar benefits which is consistent with previous study findings [24,25]. Moreover, the results of this current study revealed that only HER2-enriched patients who received adjuvant treatment using PLD-containing chemotherapy regimen and targeted therapeu-

tics obtained a lower recurrence risk, but this difference was not statistically significant. The lack of a statistically significant effect on prognosis outcome might be due to the small sample size or an inadequate follow-up interval. A comparison of pCR rates following PLD-containing neoadjuvant chemotherapy based on different molecular subtypes is shown in Table 5. The pCR rates in our study, and in other investigations, were similar in the luminal type and TNBC.

The present study also showed no benefits for distant metastatic breast cancer treated with PLD-based neoadjuvant chemotherapeutics. Similarly, the patients with lymph node metastases were also less likely to achieve pCR. Metastatic breast cancer generally has a poor prognostic outcome, and none of the treatments investigated to date, including PLD-containing chemotherapeutics, have been shown to be effective [26,27]. However, the patients with clinically negative lymph nodes was more likely to achieve pCR and showed a prognostic advantage with respect to breast cancer recurrence.

High histological grade appeared to be associated with a high pCR rate (52.9% vs 40.0%). Despite having a higher pCR rate, patients with a high histological grade still had a higher recurrence risk. High grade tumors showed a better response rate to chemotherapy in some studies [23,28]. This was probably due to better reaction to chemotherapy or possibly different subtypes of breast cancer. Invasive ductal carcinoma was the most common breast cancer type, and PLD-containing chemotherapeu-

TABLE 5.
COMPARISON OF PCR RATE BASED ON DIFFERENT MOLECULAR SUBTYPES IN THIS STUDY AND IN THE LITERATURE.

Authors	Patient numbers	pCR rate n (%)	Eligibility	Neo-adjuvant regimens
Tuxen et al. [19]	Total	48	9 (19%)	Inflammatory, LABC or large operable breast cancer (tumor >5 cm)
	Luminal	38	4 (11%)	
	HER2-enriched	3	2 (67%)	
	TNBC	7	3 (43%)	
Torrise et al. [30]	Total	32	13 (41%)	HER2 positive and T2-T4d N0-N3c M0 or M1 to the chest wall or rT1-T4a-d rN1-3, M0 or M1 to the chest wall
	Luminal	16		
	HER2-enriched	16		
Gil-Gil et al. [31]	Total	50	12 (24%)	Untreated, stage II–IIIB breast cancer, estrogen receptor (ER) below 50 %, at least one cardiotoxicity risk
	Luminal	8		
	TNBC	42		
Dong et al. [16]	Total	43	7 (16%)	Stage II to III breast cancer
	Luminal	26		
	HER2-enriched	4		
	TNBC	13		
Current research	Total	227	50 (22%)	Retrospective review, operable breast cancer
	Luminal	163	31 (19%)	
	HER2-enriched	27	10 (37%)	
	TNBC	35	9 (26%)	
	Unknown	2	0 (0%)	

Abbreviations: CPM, cyclophosphamide; HER2, human epidermal growth factor receptor; LABC, locally advanced breast cancer; pCR, pathologic complete response; PLD, pegylated liposomal doxorubicin; TNBC, triple negative breast cancer; 5FU, 5-fluorouracil

tics have shown promising results [9,19]. In this study, patients with a lower pre-chemotherapy PR rate had a better pCR rate, a result that had not been previously reported. Hence, these findings indicate that tumors with higher hormone receptors levels (pre-chemotherapy PR or ER rate) might be less responsive to chemotherapy.

For operable breast cancer patients, especially those with cardiac consideration, PLD-containing chemotherapy should be considered in neoadjuvant settings, owing to its favorable cardiotoxicity profile in other study, in order to improve the likelihood of a better prognostic outcome [16]. Previous studies have reported that PLD may cause another side effects, especially skin toxicity and mucositis, but the proportion of side effects in patients with severe grade tumors was found to be relatively low [29]. As this single institution study was retrospective in nature, some relevant variables could not be included in the analysis, which may limit the generalizability of the study results. First, the PLD-based regimen in our study lacked consistency: the treatment plans were based on physicians' preference. Second,

some patients in our institution preferred to have further treatment and follow-up in an alternate hospital after complete chemotherapy and target therapy at our institution. A longer follow-up period at our institution would have provided useful data. Third, because a previously published study had shown less cardiotoxicity with PLD-based chemotherapy [16], the cardiac function of the patients after PLD-based chemotherapy was not routinely evaluated in our institution. This evaluation would have provided useful data and would have necessitated changes to the study design. Moreover, the demographic data, including comorbidity index, performance status, body mass index and risk behaviors, as well as detailed drug and drug response information, were restricted in the database. Fourth, the current study included varied groups of patients with different molecular subtypes and stages, resulting in different treatment plans. Hence, the skewed distribution and selection bias might influence the generalizability of study outcomes. A larger prospective trial of neoadjuvant PLD-containing chemotherapeutics for operable breast cancer in Taiwan is warranted.

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REFERENCES

- Cole MP, Todd ID, Wilkinson PM. A preliminary trial of doxorubicin in advanced breast cancer and other malignant disease. *Br J Cancer*. Feb 1974;29(2):114-6.
- Ahmann DL, Bisel HF, Eagan RT, Edmonson JH, Hahn RG. Controlled evaluation of adriamycin (NSC-123127) in patients with disseminated breast cancer. *Cancer chemotherapy reports*. Nov-Dec 1974;58(6):877-82.
- Scholl SM, Asselain B, Palangie T, et al. Neoadjuvant chemotherapy in operable breast cancer. *Eur J Cancer*. 1991;27(12):1668-71.
- Pierga JY, Mouret E, Dieras V, et al. Prognostic value of persistent node involvement after neoadjuvant chemotherapy in patients with operable breast cancer. *Br J Cancer*. Dec 2000;83(11):1480-7. doi:10.1054/bjoc.2000.1461
- Early Breast Cancer Trialists' Collaborative G. Long-term outcomes for neoadjuvant versus adjuvant chemotherapy in early breast cancer: meta-analysis of individual patient data from ten randomised trials. *Lancet Oncol*. Jan 2018;19(1):27-39. doi:10.1016/S1470-2045(17)30777-5
- Kuerer HM, Newman LA, Smith TL, et al. Clinical course of breast cancer patients with complete pathologic primary tumor and axillary lymph node response to doxorubicin-based neoadjuvant chemotherapy. *J Clin Oncol*. Feb 1999;17(2):460-9. doi:10.1200/JCO.1999.17.2.460
- Kaufmann M, von Minckwitz G, Mamounas EP, et al. Recommendations from an international consensus conference on the current status and future of neoadjuvant systemic therapy in primary breast cancer. *Ann Surg Oncol*. May 2012;19(5):1508-16. doi:10.1245/s10434-011-2108-2
- Tampaki EC, Tampakis A, Alifieris CE, et al. Efficacy and Safety of Neoadjuvant Treatment with Bevacizumab, Liposomal Doxorubicin, Cyclophosphamide and Paclitaxel Combination in Locally/Regionally Advanced, HER2-Negative, Grade III at Premenopausal Status Breast Cancer: A Phase II Study. *Clinical drug investigation*. Jul 2018;38(7):639-648. doi:10.1007/s40261-018-0655-z
- Sparano JA, Makhson AN, Semiglazov VF, et al. Pegylated liposomal doxorubicin plus docetaxel significantly improves time to progression without additive cardiotoxicity compared with docetaxel monotherapy in patients with advanced breast cancer previously treated with neoadjuvant-adjuvant anthracycline therapy: results from a randomized phase III study. *J Clin Oncol*. Sep 20 2009;27(27):4522-9. doi:10.1200/JCO.2008.20.5013
- Gabizon A, Shmeeda H, Grenader T. Pharmacological basis of pegylated liposomal doxorubicin: impact on cancer therapy. *European journal of pharmaceutical sciences : official journal of the European Federation for Pharmaceutical Sciences*. Mar 12 2012;45(4):388-98. doi:10.1016/j.ejps.2011.09.006
- Gabizon AA, Lyass O, Berry GJ, Wildgust M. Cardiac safety of pegylated liposomal doxorubicin (Doxil/Caelyx) demonstrated by endomyocardial biopsy in patients with advanced malignancies. *Cancer Invest*. 2004;22(5):663-9.
- Gabizon A, Shmeeda H, Barenholz Y. Pharmacokinetics of pegylated liposomal Doxorubicin: review of animal and human studies. *Clinical pharmacokinetics*. 2003;42(5):419-36. doi:10.2165/00003088-200342050-00002
- Gabizon AA, Patil Y, La-Beck NM. New insights and evolving role of pegylated liposomal doxorubicin in cancer therapy. *Drug resistance updates : reviews and commentaries in antimicrobial and anticancer chemotherapy*. Nov 2016;29:90-106. doi:10.1016/j.drug.2016.10.003
- Yang FO, Hsu NC, Moi SH, et al. Efficacy and toxicity of pegylated liposomal doxorubicin-based chemotherapy in early-stage breast cancer: a multicenter retrospective case-control study. *Asia-Pacific journal of clinical oncology*. Jun 2018;14(3):198-203. doi:10.1111/ajco.12771
- Chang AE, Wu QV, Jenkins IC, et al. Phase I/II Trial of Combined Pegylated Liposomal Doxorubicin and Cyclophosphamide in Metastatic Breast Cancer. *Clin Breast Cancer*. Feb 2018;18(1):e143-e149. doi:10.1016/j.clbc.2017.10.005
- Dong M, Luo L, Ying X, et al. Comparable efficacy and less toxicity of pegylated liposomal doxorubicin versus epirubicin for neoadjuvant chemotherapy of breast cancer: a case-control study. *Oncotargets and therapy*. 2018;11:4247-4252. doi:10.2147/OTT.S162003
- Green MC, Buzdar AU, Smith T, et al. Weekly paclitaxel improves pathologic complete remission in operable breast cancer when compared with paclitaxel once every 3 weeks. *J Clin Oncol*. Sep 1 2005;23(25):5983-92. doi:10.1200/JCO.2005.06.232
- Loibl S, de la Pena L, Nekljudova V, et al. Neoadjuvant buparlisib plus trastuzumab and paclitaxel for women with HER2+ primary breast cancer: A randomised, double-blind, placebo-controlled phase II trial (NeoPHOEBE). *Eur J Cancer*. Nov 2017;85:133-145. doi:10.1016/j.ejca.2017.08.020
- Tuxen MK, Cold S, Tange UB, Balslev E, Nielsen DL. Phase II study of neoadjuvant pegylated liposomal doxorubicin and cyclophosphamide +/- trastuzumab followed by docetaxel in locally advanced breast cancer. *Acta Oncol*. Oct 2014;53(10):1440-5. doi:10.3109/0284186X.2014.921727

20. Artioli G, Mocellin S, Borgato L, et al. Phase II study of neo-adjuvant gemcitabine, pegylated liposomal doxorubicin, and docetaxel in locally advanced breast cancer. *Anticancer Res*. Sep 2010;30(9):3817-21.
21. Rossi D, Baldelli AM, Casadei V, et al. Neoadjuvant chemotherapy with low dose of pegylated liposomal doxorubicin plus weekly paclitaxel in operable and locally advanced breast cancer. *Anticancer Drugs*. Aug 2008;19(7):733-7. doi:10.1097/CAD.0b013e3283043585
22. Gogas H, Papadimitriou C, Kalofonos HP, et al. Neoadjuvant chemotherapy with a combination of pegylated liposomal doxorubicin (Caelyx) and paclitaxel in locally advanced breast cancer: a phase II study by the Hellenic Cooperative Oncology Group. *Annals of oncology : official journal of the European Society for Medical Oncology*. Nov 2002;13(11):1737-42.
23. Kurozumi S, Inoue K, Takei H, et al. ER, PgR, Ki67, p27(Kip1), and histological grade as predictors of pathological complete response in patients with HER2-positive breast cancer receiving neoadjuvant chemotherapy using taxanes followed by fluorouracil, epirubicin, and cyclophosphamide concomitant with trastuzumab. *BMC Cancer*. Sep 7 2015;15:622. doi:10.1186/s12885-015-1641-y
24. Davidson NE, O'Neill AM, Vukov AM, et al. Chemoendocrine therapy for premenopausal women with axillary lymph node-positive, steroid hormone receptor-positive breast cancer: results from INT 0101 (E5188). *Journal of clinical oncology*. 2005;23(25):5973-5982.
25. Cejalvo JM, Pascual T, Fernández-Martínez A, et al. Clinical implications of the non-luminal intrinsic subtypes in hormone receptor-positive breast cancer. *Cancer treatment reviews*. 2018;67:63-70.
26. Takiar V, Akay CL, Stauder MC, et al. Predictors of durable no evidence of disease status in de novo metastatic inflammatory breast cancer patients treated with neoadjuvant chemotherapy and post-mastectomy radiation. *Springerplus*. 2014;3:166. doi:10.1186/2193-1801-3-166
27. Murthy RK, Varma A, Mishra P, et al. Effect of adjuvant/neoadjuvant trastuzumab on clinical outcomes in patients with HER2-positive metastatic breast cancer. *Cancer*. Jul 1 2014;120(13):1932-8. doi:10.1002/cncr.28689
28. Lips EH, Mulder L, de Ronde JJ, et al. Breast cancer subtyping by immunohistochemistry and histological grade outperforms breast cancer intrinsic subtypes in predicting neoadjuvant chemotherapy response. *Breast Cancer Res Treat*. Jul 2013;140(1):63-71. doi:10.1007/s10549-013-2620-0
29. Ansari L, Shiehazadeh F, Taherzadeh Z, et al. The most prevalent side effects of pegylated liposomal doxorubicin monotherapy in women with metastatic breast cancer: a systematic review of clinical trials. *Cancer gene therapy*. 2017;24(5):189-193.
30. Torrisi R, Cardillo A, Cancellio G, et al. Phase II trial of combination of pegylated liposomal doxorubicin, cisplatin, and infusional 5-fluorouracil (CCF) plus trastuzumab as preoperative treatment for locally advanced and inflammatory breast cancer. *Clin Breast Cancer*. Dec 1 2010;10(6):483-8. doi:10.3816/CBC.2010.n.064
31. Gil-Gil MJ, Bellet M, Morales S, et al. Pegylated liposomal doxorubicin plus cyclophosphamide followed by paclitaxel as primary chemotherapy in elderly or cardiotoxicity-prone patients with high-risk breast cancer: results of the phase II CAPRICE study. *Breast Cancer Res Treat*. Jun 2015;151(3):597-606. doi:10.1007/s10549-015-3415-2