

The Efficacy and Safety of Gemcitabine Plus Paclitaxel Compared to Doxorubicin Plus Cyclophosphamide as Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer

Abstract

Background: Neoadjuvant chemotherapy is now considered current practice for patients with locally advanced breast cancer. This two-arm randomized clinical study aims to compare the efficacy and safety of gemcitabine plus paclitaxel with doxorubicin plus cyclophosphamide as neoadjuvant chemotherapy in locally advanced breast cancer.

Methods: Eligible women with newly pathologically diagnosed locally advanced breast cancer were randomly assigned to receive 4 cycles of neoadjuvant chemotherapy with doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) (AC arm) or gemcitabine (1000 mg/m² days 1 and 8) and paclitaxel (175 mg/m²) (GP arm) every three weeks. Clinical and radiological tumor measurements were performed before and after intervention. Subsequently, all the patients underwent mastectomy after the fourth cycle of neoadjuvant chemotherapy and then crossed over to receive the other treatment arm as adjuvant therapy.

Results: Sixty-six patients in both arms (AC, n=34; and GP, n=32) completed the study. Before intervention, the mean clinical maximum diameter tumor size was 7.9 cm and 7.1 cm in AC and GP arms respectively. After intervention, these values were decreased to 5.1 cm and 4.2 cm respectively. Pathologic complete response rates were 29.5% and 0.0% in the AC and the GP arm, respectively (P = 0.001). However, there was no statistically difference regarding the rate of clinical and radiologic responses in AC arm compared to the GP arm. As well, there was no statistical significant difference regarding treatment-related toxicity.

Conclusion: This study suggest that in patients with locally advanced breast cancer, the addition of gemcitabine to paclitaxel in neoadjuvant setting does not provide any superiority in terms of clinical and/or pathological response rate or toxicity profile compared to the AC regimen.

Keywords: Breast cancer; Neoadjuvant treatment; Chemotherapy; Efficiency; Gemcitabine

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**Niloofar Ahmadloo¹, Leila Moaddabshoar²,
Hamid Nasrolahi¹, Shapour Omidvari³,
Sayed Hasan Hamed¹, Ahmad Mosalaei⁴,
Mansour Ansari¹ and Mohammad
Mohammadianpanah^{5*}**

¹Department of Radiation Oncology, Shiraz University of Medical Sciences, Iran

²Department of Radiation Oncology, Shiraz University of Medical Sciences, Iran

³Breast Diseases Research Center, Shiraz University of Medical Sciences, Iran

⁴Shiraz Institute for Cancer Research, Iran

⁵Department of Radiation Oncology, Colorectal Research Center, Shiraz University of Medical Sciences, Iran

***Corresponding author:** Mohammad Mohammadianpanah, Colorectal Research Center, Department of Radiation Oncology, Shiraz University of Medical Sciences, Shiraz 71936, Iran, Tel: +98 713 6125170; Fax: +98 713 6474320; Email: mohpanah@gmail.com; mohpanah@sums.ac.ir

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Introduction

Breast cancer is the most prevalent cancer among women worldwide and its incidence is increasing [1,2]. Combination chemotherapy has brought patients a significant improvement in survival [2,3]. Despite advances in chemotherapy, breast cancer is the leading cause of cancer related death among women [1]. Distant failure is the major problem in breast cancer patients. When metastasis occurs, chemotherapy is usually necessary beside endocrine therapy. In that case, combination chemotherapy is more effective than single agent treatment [1,4,5]. Combination of cyclophosphamide, methotrexate and 5-fluorouracil (CMF regimen) was a standard chemotherapy for years. Years later, doxorubicin was found to be more effective in metastatic patients and then in adjuvant patients [6]. According to multiple studies, anthracycline replaced methotrexate in CMF regimen. Later, taxanes were added to this combination chemotherapy and 5-fluorouracil was omitted. Various combinations and sequences have been studied to find the most effective and safe combination regimen [3,7-9].

Various chemotherapy agents have been tested in breast cancer metastasis. Gemcitabine has a well-established effect in metastatic breast cancer [2]. Gemcitabine produces 37% and 26% response rate in the first line and in pretreated metastatic breast cancer patients [4]. Gemcitabine is well tolerated in combination with paclitaxel and has no serious complications [4]. Multiple studies have evaluated the effectiveness and side effects of this combination chemotherapy. Gemcitabine combined with Paclitaxel (GP) has been shown to be both effective and safe [1].

We conducted this phase III controlled randomized clinical trial to compare the efficacy of GP with AC on tumor response and evaluate treatment-related side effects.

Methods and Materials

Eligibility criteria

Eligible patients were required to have newly pathologically diagnosed locally advanced (clinical stage T3, T4 and/or N2, N3) breast cancer. Other Eligibility Criteria were clinically and

radiologic measurable disease, good Karnofsky performance status (KPS>70) and normal liver, kidney and bone marrow function. Exclusion criteria were metastatic disease, history of previous chemotherapy or other cancers and other severe comorbidities such as heart problem or diabetes mellitus. Hypersensitivity reaction to chemotherapy agents was also an exclusion criterion.

Study design

This controlled randomized clinical trial was conducted to compare clinical, radiologic and pathologic response rates of two chemotherapy regimens between Jan 2012 to Dec 2013. The trial was approved by the local university ethics committee in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki. Preliminary evaluation including delicate history taking and physical exam, abdomen-pelvic and chest CT scan, bone scan and blood tests (CBC, LFT, BUN and Cr) were performed for all patients. Eligible patients had to sign a consent form before participating in the study. Thereafter, the patients were randomly assigned to receive 4 cycles of neoadjuvant chemotherapy with doxorubicin (60 mg/m²) and cyclophosphamide (600 mg/m²) (AC arm) every three weeks; or gemcitabine (1000 mg/m² days 1 and 8) and paclitaxel (175 mg/m²) (GP arm) every three weeks. Subsequently, all the patients underwent mastectomy after the fourth cycle of neoadjuvant chemotherapy and then crossed over to receive the other treatment arm as adjuvant therapy.

Study evaluation

All patients underwent whole body bone scan and abdominal, pelvic and chest CT scans before starting intervention. Blood tests (CBC, RFT and LFT) were performed within a week before treatment and before each cycle of chemotherapy. Bilateral breast and axilla sonography was performed before the first and after

the 4th chemotherapy injection. A single expert radiologist in our hospital did all radiologic evaluations, whom was also blinded to the type of chemotherapy. Clinical tumor measurements was carried out and documented by 2 different oncologists in duplicate. They were blinded to the type of treatment and each other's measurements. The largest tumor size was measured by caliper. Tumor response was measured according to the Response Evaluation Criteria In Solid Tumors (RECIST) [10]. Complete response was defined as no evidence of residual tumor; partial response as more than 30% tumor size decrement. Less than 30% decrease or less than 20% increase in tumor dimension was considered no response. Tumor progression was increasing more than 20% tumor dimension.

Statistical evaluation

To compare the clinical, radiological and pathological response rates and the clinicopathologic characteristics of the trial arms, the Chi-square (x²), Fisher's exact and Mann-Whitney tests were used. According to previous studies, a minimum sample size required 30 patients in each arm to insure 80% power at the 5% significance level for detecting a 22% improvement in the clinical complete, radiological and pathological response rates from 8% to 30%. All statistical tests were two-sided and P values less than 0.05 were considered significant. SPSS version 17.0 software (SPSS, Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Among patients who were referred for neoadjuvant chemotherapy for breast cancer, 70 cases were eligible and randomly assigned from Jan 2012 to Dec 2013. Thirty-five to AC and other 35 patients to GP. One case stopped her treatment because of nausea and vomiting in AC arm. Three patients in the GP arm refused chemotherapy due to musculoskeletal pain after the first cycle of chemotherapy (Figure 1).

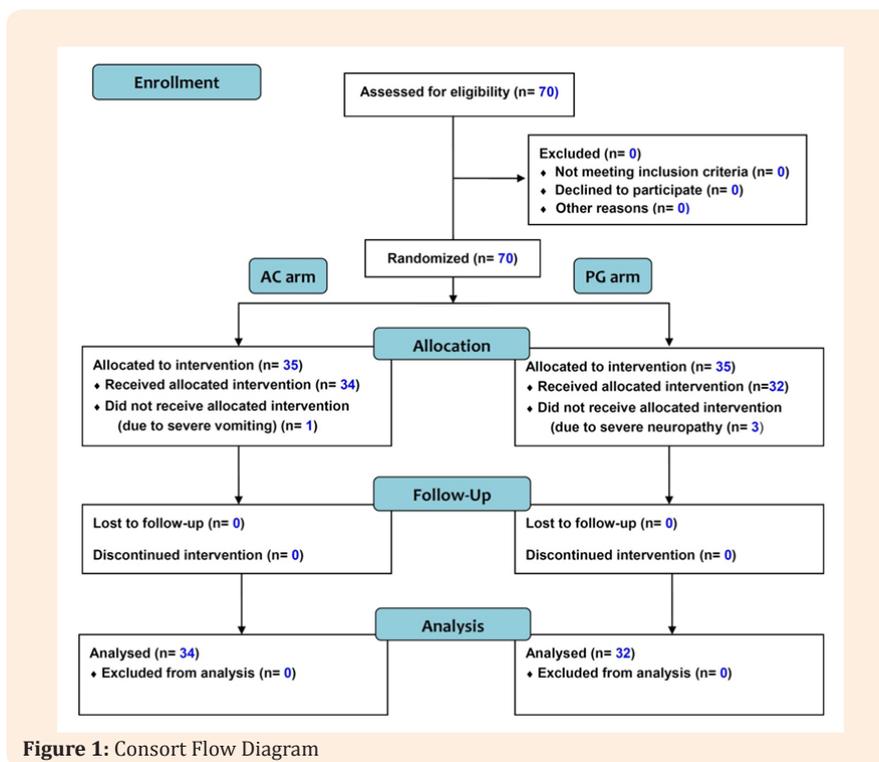


Figure 1: Consort Flow Diagram

Patients' characteristics

All patients were Iranian ethnicity and median age was 45.3 (28-70) years. In the AC and GP arms, median ages were 47.4 (32-70) and 43.2 (28-68) years, respectively. The difference was not statistically significant.

Tumor characteristics

Clinical tumor size was larger in the AC arm, but this difference was not statistically significant. The mean clinical maximum diameter tumor size was 7.9 cm and 7.1 cm in the AC and GP arms respectively. After intervention, these values were decreased to 5.1 cm and 4.2 cm respectively. Before starting treatment and using ultrasound measurement, the maximum radiologic tumor size diameter was 4.1 cm in AC arm and 4.6 cm in the GP arm. (Table 1)

Efficacy

Clinical response

During the chemotherapy, the maximum clinical tumor sizes decreased. In the AC arm, in weeks 3, 6 and 9 maximum clinical tumor diameter were 6.7cm, 5.8 cm and 5.1 cm respectively. In the GP arm, tumor sizes were 5.9 cm, 4.9 cm, and 4.2 cm in weeks 3, 6 and 9 respectively. (Table 1) These differences between the two arms were not statically significant (P value=0.56).

Complete clinical response was not seen in any patients the GP arm, while in the AC arm 10 (29.5%) patients showed complete response. Partial response rate was higher in the GP arm (75% versus 52.9%). None of the patients in the AC arm exhibited tumor progression, however two (6.2%) of those who received GP showed tumor progression. Six patients in each arm showed no significant change in tumor size. The statistical differences between treatment arms were not significant. (Table 2)

Table 1: Clinical, radiological and pathological tumor size (cm) in treatment arms.

Characteristics	AC	GP	P value
Mean Age (range)	47.4 (32-70)	43.2 (28-68)	
Clinical Tumor Size (mean ± SD)			
Day 0	7.9 ± 1.7	7.13 ± 1.8	>0.05
Tumor Size Day 21	7.8 ± 1.7	7.1 ± 1.8	
Tumor Size Day 42	6.7 ± 1.6	5.9 ± 1.8	
Tumor Size Day 63	5.8 ± 1.6	4.9 ± 1.8	
Before Operation	5.1 ± 1.7	4.2 ± 1.7	0.56
Radiologic Diameter (mean ± SD)			
Day 0	4.1 ± 2.71	4.6 ± 1.6	0.76
Day 84	2.5 ± 1.4	3.2 ± 2.3	
Pathologic Diameter	3.0 ± 3.00	3.41 ± 2.6	0.57

SD: Standard Deviation

Table 2: Clinical, radiological and pathological response rates in treatment arms.

Treatment Response	AC	GP	Total	P value
Clinical Response Rates				
Complete	10 (29.5%)	0 (0%)	10 (15.2%)	0.54
Partial	18 (52.9%)	24 (75%)	42 (63.6%)	
No Response	6 (17.6%)	6 (18.8)	12 (18.2%)	
Progression	0 (0%)	2 (6.2%)	2 (3%)	
Radiologic Response Rates				
Complete	9 (26.5%)	0 (0%)	9 (13.6%)	0.42
Partial	16 (47%)	23 (71.9%)	39 (59.1%)	
No Response	8 (23.5%)	6 (18.8%)	14 (21.2%)	
Progression	1 (3%)	3 (8.3%)	4 (6.1%)	
Pathologic Response Rates				
Complete Response	10	0	10	0.001 ^a
No Complete Response	24	32	46	

^a: Fisher's Exact Test

Prior to starting chemotherapy and after the fourth chemotherapy cycle, breast sonography was performed for all patients. As shown in Table 1, there was no significant difference between the two arms before and after chemotherapy.

After the last chemotherapy cycle, these diameters were 2.5 and 3.2 cm in the AC and GP arms, respectively. This difference was not statistically significant. Radiologic responses in two arms were not different. Complete response in the AC arm was 26.5% (9 patients) while no patients in the GP arm showed complete response in radiologic evaluation. In contrast, partial tumor response was more frequent in the GP arm. In GP arm, 23 patients (71.9%) partially responded to chemotherapy; while, 16 patients (47%) partially responded in the AC arm. Tumor progression was more frequent in the GP arm than the AC arm (8.3% versus 3%). However, radiologic tumor response rates were not statistically different between the two arms.

Pathologic response

After four cycles of chemotherapy, surgical operation was performed for all patients. Mean pathologic tumor size in AC arm was 3 cm, while in GP arm pathologic tumor size was 3.4 cm. Pathologic complete response rates were 29.5% and 0.0% in the AC and the GP arm, respectively ($P = 0.001$).

Side effects

Regarding side effects, grade III-IV nausea and vomiting was more prevalent in the AC arm (85% versus 25%) and this difference was statistically significant (P value < 0.05). However, nausea and vomiting did not cause delay in chemotherapy and all were managed successfully. One case (3%) of grade III neutropenia was also seen in each arm but no grade III-IV anemia or thrombocytopenia was observed. For these 2 patients, chemotherapy were continued after 1 week delay. All patients in both arms developed grade I or II alopecia.

Discussion

Despite an increase in breast cancer incidence, its mortality has decreased. The reason of this reduction may be attributed to advances in chemotherapy. Currently, anthracyclin- and taxane-based combination chemotherapy is considered as standard regimen in patients with locally advanced breast cancer [11]. Despite improvement in adjuvant therapies, when metastasis occurs, the patient is not considered curable [12,1]. Therefore, it is necessary to search for treatments that are more effective.

Gemcitabine is an antimetabolite anti-cancer agent. It is activated after entering cells and then interferes with DNA synthesis [13]. Carmichael et al in 1995 in a phase II study on 44 patients with locally advanced or metastatic breast cancer administered Gemcitabine as a single agent chemotherapy. Overall response rate in that study was 25% and side effects were manageable. Other studies confirmed effectiveness and tolerability of Gemcitabine in breast cancer [14,15].

Gemcitabine and paclitaxel may have synergistic antitumor effects [1,13]. Tomao et al in a phase II study administered Paclitaxel and Gemcitabine combination chemotherapy. Their patients had primary or metastatic measurable breast cancer. In their study, gemcitabine was administered in a dose of two gr/m²

and Paclitaxel in 150 mg/m², every 2 weeks. Among 25 patients, 16 patients (64%) responded to the treatment. Complete response was observed in four patients (16%) and four remaining patients (16%) had progressive disease. No treatment-related mortality occurred and main toxicities were hematologic (leucopenia, anemia and thrombocytopenia). Two patients developed grade 4 neutropenia and one patient grade 4 thrombocytopenia [12]. The safety and effectiveness of combination chemotherapy with GP was confirmed in other phase II studies [16-18].

Sanchez-Munoz et al in a prospective study on 73 patients, administered dose dense epirubicin and cyclophosphamide sequentially with GP regimen. After operation, 37% of patients showed complete pathologic response. Complete response was more frequent in Her2 negative, poor differentiated and positivity of Ki-67 and P53. The most common toxicities were neutropenia (12%), and nausea and vomiting (17%). They suggested this combination chemotherapy as a good choice with manageable side effects [19]. Gemcitabine and paclitaxel combination chemotherapy has been approved for patients who were previously treated by anthracycline-based combinations [20].

In order to improve the response and survival rates, some researchers added gemcitabine to routine (doxorubicin- and paclitaxel-based) regimens in the first line treatment of non-metastatic patients. Earl et al. [2] in a large multicenter study compared the standard treatment with addition of gemcitabine to chemotherapy. Four arms were included in their study; usual chemotherapy combination with epirubicin and cyclophosphamide (EC) followed by paclitaxel (P), P followed by EC. In two other arms, gemcitabine was combined with P in the standard regimens. In their study, 416 patients received gemcitabine in addition to standard treatment. The addition of gemcitabine had no effect on complete response (17% in both arms) [2]. Pathologic complete response and survival rates were the first and the second endpoints of the study. The addition of gemcitabine and sequence of chemotherapy administration had no effect on survival. Attractively, those who had received paclitaxel before anthracycline-based chemotherapy showed a better complete pathologic response. This better response was independent of gemcitabine administration [2].

Albain et al in a phase III metacentric study on 529 patients with measurable metastasis or recurrence compared P and GP. In GP arm, patients received 1250 mg/m² gemcitabine in days 1, 8 and 175 mg/m² paclitaxel. Another arm only received paclitaxel 175 mg/m² on day 1. Radiologic response was significantly higher in the GP arm (43.1% and 26.9%; $P = 0.0007$). Complete response was seen in 7.9% of patients in the GP and 4.6% in the P arm. Overall response was significantly higher in the GP arm (41.4% versus 26.2% P value = 0.0002). In metastatic patients, GP combination produces a significant and durable response comparing to P alone. The main grade 3-4 toxicity was neutropenia that occurred in 47.9% of patients in the GP arm and 11.5% of patients in the P arm. Febrile neutropenia was also more common in the GP arm (5% versus 1.2%). In addition, anemia and thrombocytopenia were more prevalent in GP arm. Overall survival in GP arm was longer (18.6 versus 15.8 months, $P=0.0493$). Time to tumor progression (TTP) was also significantly longer in the GP vs. P arm (6.14 versus 3.98 months, $P = .0002$). OS improved by 22%

and TTP by 43% [1]. We used the same GP dose and schedule. Comparing our study with only 3% grade III neutropenia, it seems that prophylactic hematologic support is necessary. In the present study, no (neither clinical nor pathologic) complete response was observed in the GP arm.

While the above-mentioned studies support the addition of G, some others are not so. In a meta-analysis of nine randomized controlled trials (encompassing 2651 patients), Li et al concluded that gemcitabine has no benefit when is added to combination chemotherapy in metastatic breast cancer patients. Gemcitabine did not improve overall response rate, time to tumor progression and overall survival. Gemcitabine increased grade 3-4 toxicities including anemia, neutropenia and thrombocytopenia [21].

In a prospective study on 4894 patients with non-metastatic breast cancer, Swain et al tested the addition of gemcitabine to standard chemotherapy regimens. They added gemcitabine to paclitaxel in AC followed by P regimens. In their study, patients received two standard regimens, TAC and dose dense AC followed by P in two arms. Another arm received dose dense AC and then dose dense paclitaxel combined with gemcitabine. After 5 years, disease free and overall survival was not different in three arms. Febrile neutropenia and diarrhea were more frequent in TAC arm and neuropathy was more frequent in dose dense regimens [22].

It seems that gemcitabine is more effective in metastatic or recurrent breast cancer, compared to the first line treatment.

Conclusion

The results of this study suggest that in patients with locally advanced breast cancer, the addition of gemcitabine to paclitaxel in neoadjuvant setting does not provide any superiority in terms of clinical and/or pathological response rate or toxicity profile compared to the AC regimen.

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References

1. Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, et al. (2008) Gemcitabine plus Paclitaxel versus Paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol* 26(24): 3950-3957.
2. Earl HM, Vallier AL, Hiller L, Fenwick N, Young J, et al. (2014) Effects of the addition of gemcitabine, and paclitaxel-first sequencing, in neoadjuvant sequential epirubicin, cyclophosphamide, and paclitaxel for women with high-risk early breast cancer (Neo-tAnGo): an open-label, 2x2 factorial randomised phase 3 trial. *The lancet oncology* 15(2): 201-212.
3. Martin M, Pienkowski T, Mackey J, Pawlicki M, Guastalla JP, et al. (2005) Adjuvant docetaxel for node-positive breast cancer. *N Engl J Med* 352(22): 2302-2313.
4. Allouache D, Gawande SR, Tubiana-Hulin M, Tubiana-Mathieu N, Piperno-Neumann S, et al. (2005) First-line therapy with gemcitabine and paclitaxel in locally, recurrent or metastatic breast cancer: a phase II study. *BMC cancer* 5: 151.
5. D Del Mastro L, Fabi A, Mansutti M, De Laurentiis M, Durando A, et al. (2013) Randomised phase 3 open-label trial of first-line treatment with gemcitabine in association with docetaxel or paclitaxel in women with metastatic breast cancer: a comparison of different schedules and treatments. *BMC cancer* 13: 164.
6. Omidvari S, Hosseini S, Ashouri Y, Tahmasebi S, Talei A, Nasrolahi H, et al. (2011) Comparison of Docetaxel, Doxorubicin and Cyclophosphamide (TAC) with 5-Fluorouracil, Doxorubicin and Cyclophosphamide (FAC) Neoadjuvant Chemotherapy in Locally Advanced Breast Cancer: A Phase III Clinical Trial. *Middle East Journal of Cancer* 2(2): 51-58.
7. Piedbois P, Serin D, Priou F, Laplaige P, Greget S, et al. (2007) Dose-dense adjuvant chemotherapy in node-positive breast cancer: docetaxel followed by epirubicin/cyclophosphamide (T/EC), or the reverse sequence (EC/T), every 2 weeks, versus docetaxel, epirubicin and cyclophosphamide (TEC) every 3 weeks. AERO B03 randomized phase II study. *Ann Oncol* 18(1): 52-57.
8. Cole MP, Todd ID, Wilkinson PM (1974) A preliminary trial of doxorubicin in advanced breast cancer and other malignant disease. *Br J Cancer* 29(2): 114-116.
9. Mohammadianpanah M, Ashouri Y, Hoseini S, Amadloo N, Talei A, et al. (2012) The efficacy and safety of neoadjuvant chemotherapy +/- letrozole in postmenopausal women with locally advanced breast cancer: a randomized phase III clinical trial. *Breast Cancer Res Treat* 132(3): 853-861.
10. Eisenhauer EA, Therasse P, Bogaerts J, Schwartz LH, Sargent D, Ford R, et al. (2009) New response evaluation criteria in solid tumours: revised RECIST guideline (version 1.1). *European journal of cancer* 45(2): 228-247.
11. Wardley AM, Hiller L, Howard HC, Dunn JA, Bowman A, et al. (2008) tAnGo: a randomised phase III trial of gemcitabine in paclitaxel-containing, epirubicin/cyclophosphamide-based, adjuvant chemotherapy for early breast cancer: a prospective pulmonary, cardiac and hepatic function evaluation. *Br J Cancer* 99(4): 597-603.
12. Tomao S, Romiti A, Tomao F, Di Seri M, Caprio G, et al. (2006) A phase II trial of a biweekly combination of paclitaxel and gemcitabine in metastatic breast cancer. *BMC cancer* 6: 137.
13. Amadori D, Cecconetto L (2006) Gemcitabine and taxanes in metastatic breast cancer. *Annals of Oncology* 17(5): v173-v176.
14. Carmichael J, Possinger K, Phillip P, Beykirch M, Kerr H, et al. (1995) Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol* 13(11): 2731-2736.
15. Possinger K, Kaufmann M, Coleman R, Stuart NS, Helsing M, et al. (1999) Phase II study of gemcitabine as first-line chemotherapy in patients with advanced or metastatic breast cancer. *Anticancer drugs* 10(2): 155-162.
16. Colomer R, Llombart-Cussac A, Lluch A, Barnadas A, Ojeda B, et al. (2004) Biweekly paclitaxel plus gemcitabine in advanced breast cancer: phase II trial and predictive value of HER2 extracellular domain. *Ann Oncol* 15(2): 201-206.
17. Murad AM, Guimaraes RC, Aragao BC, Scalabrini-Neto AO, Rodrigues VH (2001) Phase II trial of the use of paclitaxel and gemcitabine as a salvage treatment in metastatic breast cancer. *Am J Clin Oncol* 24(3): 264-268.
18. Delfino C, Caccia G, Gonzáles LR, Mickiewicz E, Rodger J, et al. (2004)

- Gemcitabine plus paclitaxel as first-line chemotherapy for patients with advanced breast cancer. *Oncology* 66(1): 18-23.
19. Sánchez-Muñoz A1, Dueñas-García R, Jaén-Morago A, Carrasco E, Chacón I, et al. (2010) Is it possible to increase pCR in the neoadjuvant treatment with a dose-dense/sequential combination?: results from a phase II Trial combining epirubicin and cyclophosphamide followed by paclitaxel and gemcitabine +/- trastuzumab in stage II and III breast cancer patients. *American journal of clinical oncology* 33(5): 432-437.
20. Metro G, Zheng Z, Fabi A, Schell M, Antoniani B, et al. (2010) In situ protein expression of RRM1, ERCC1, and BRCA1 in metastatic breast cancer patients treated with gemcitabine-based chemotherapy. *Cancer Invest* 28(2): 172-180.
21. Li W, Wang H, Li X (2013) Efficacy of gemcitabine-based chemotherapy in metastatic breast cancer: a meta-analysis of randomized controlled trials. *Curr Med Res Opin* 29(11): 1443-1452.
22. Swain SM, Tang G, Geyer CE Jr, Rastogi P, Atkins JN, et al. (2013) Definitive results of a phase III adjuvant trial comparing three chemotherapy regimens in women with operable, node-positive breast cancer: the NSABP B-38 trial. *J Clin Oncol* 31(26): 3197-3204.