

Research Article

Paclitaxel plus Gemcitabine as Second Line Chemotherapy for Patients with Metastatic or Locally Advanced Breast Cancer - A Phase II Study

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Objective: The combination of paclitaxel and gemcitabine (PG) has been proposed as a promising combination as second line chemotherapy in metastatic breast cancer (MBC). We assessed the efficacy and toxicity of PG in a split-dose schedule in a phase II study.

Methods: Forty-two patients were enrolled in the study. Treatment consisted of paclitaxel 80 mg/m² and gemcitabine 1000 mg/m², both administered day 1 and 8 every 21 days. Patients had MBC or locally advanced breast cancer. The primary endpoint was response rate (RR). Secondary endpoints were time to progression (TTP), overall survival (OS), toxicity and clinical benefit rate (CBR).

Results: Median age was 56.5 years. Eight patients (19.0%) received epirubicin in the adjuvant setting. Thirty patients (71.4%) were previously treated with epirubicin in the metastatic setting. The RR was 25% (95% CI, 12.7-41.2%) and the CBR was 47.5% (95% CI, 31.5-63.9%). Median TTP was 4.9 months (95% CI, 3.2-6.5 months) and the median OS was 10.6 months (95% CI, 8.3-12.9 months). The toxicity was modest. CTC grade 3 and 4 neutropenia was seen in 17 patients (40.5%). One patient (2.4%) had febrile neutropenia.

Conclusion: The RR, TTP and OS were lower when compared to other studies of these two drugs in combination. This present study was comparable in toxicity to other studies and is maybe comparable in efficacy, but it did not bring any reason to believe a benefit in neither efficacy nor toxicity could be achieved in the combination by splitting the paclitaxel into two doses.

Keywords: Breast cancer; Gemcitabine; Paclitaxel; Phase II

Introduction

Breast cancer is one of the most common malignancies affecting women with an estimated 1.67 million new cases worldwide annually [1]. In spite of advantages in the adjuvant setting in the last decades, more than twenty percent of women diagnosed with early breast cancer will eventually develop metastatic disease [2]. Generally metastatic breast cancer (MBC) is considered incurable with a median survival of 20-24 months, highly influenced by factors as age, performance status, location and numbers of metastasis and duration of disease free interval [3]. The main aims of treatment are alleviation of symptoms, optimizing quality of life and prolongation of life. The overall response rate (RR) for first line chemotherapy in MBC, is in the range of 40-60%, yielding modest RR in later lines [4]. Chemotherapy is the first choice of treatment for patients with hormone resistant, hormone receptor negative disease or in case of significant visceral involvement [4].

Anthracyclines and taxanes are generally considered the most effective chemotherapy in the metastatic setting, but since these are an integral part of adjuvant treatment, it limits the later use of these drugs. This is in part due to the cumulative cardiotoxicity of anthracyclines [4]. Thus, there is need for studies to evaluate other possible treatments of patients with MBC that is considered

anthracycline resistant.

The combination of paclitaxel and gemcitabine is interesting because of different mechanisms of action, without proven shown cross resistance and with different toxicity profiles [4-6]. Paclitaxel and gemcitabine have both shown efficacy in MBC showing RR in phase II studies of 21% to 53% [7-13] and 14% to 42% [14-17], respectively. A phase II study of split-dose paclitaxel plus gemcitabine was conducted to evaluate efficacy, time to progression (TTP), overall survival (OS) and safety.

Materials and Methods

Study design

This study was a phase II study of paclitaxel plus gemcitabine in patients with MBC or locally advanced breast cancer (LABC). Treatment consisted of paclitaxel 80 mg/m², administered as a 60-minute intravenous (IV) infusion day 1 and 8 plus gemcitabine 1000 mg/m² as a 30-minute IV infusion day 1 and 8 every 21 days. All patients were pre medicated 30 minutes prior to chemotherapy with dexamethasone 10 mg IV, clemastine 2 mg IV and cimetidine 300 mg IV.

Treatment continued until progression, unacceptable toxicity, or withdrawal of consent.

Eligibility criteria

Women, aged 18-75, with histologically or cytologically confirmed MBC (stage IV or recurrent) or LABC, were eligible for the study. Prior endocrine therapy in the adjuvant or metastatic setting was allowed. Chemotherapy in the adjuvant setting and one prior regime of chemotherapy in the metastatic setting were allowed. At least one measurable lesion was required. Other eligibility criteria included a life expectancy of more than three month, Eastern Cooperative Oncology Group (ECOG) PS0-2, adequate bone marrow, renal, and liver function. Patients were ineligible if pregnant or breastfeeding, or if they had another concurrent or previous malignant neoplasm (within 5 years). Exceptions were made for adequately controlled in situ uterine carcinoma and/or cutaneous basal cell carcinoma. Premenopausal patients were eligible provided they used reliable contraceptive methods. Exclusion criteria also included NCI Common Toxicity Criteria 2.0 (CTC) grade 2 or greater peripheral neuropathy or clinically detectable brain metastases, prior treatment with taxanes or gemcitabine, previous allergic reaction to medications containing cremophor, severe psychiatric or medical conditions, severe ongoing infection and active cardiac disease not controlled by therapy and/or myocardial infarction within the last year prior to inclusion. Chemotherapy up to 4 weeks prior to inclusion was allowed. Written, informed consent was obtained from all patients before entering the study. The study was conducted in accordance with the Declaration of Helsinki. The protocol was approved by the Local Ethics Committees (Copenhagen County no. KA00036gs).

Baseline and treatment assessments

Radiological tests, medical history, physical examination, electrocardiography, blood test, pregnancy test and neurologic examination were performed within 2 weeks prior to first treatment.

Before day 1 in a new cycle physical examination and blood tests were performed. Before day 8 and 15 blood tests were done and toxicities were assessed before every treatment using NCI CTC version 2.0. Tumor measurements were scheduled after every three cycles for lesions assessed radiographically. The RECIST 1.0 criteria were used for response evaluation [18]. Patients were considered feasible for response evaluation, if they had received at least one cycle of treatment.

Dose modifications

Treatment at day 1 was delayed if absolute neutrophile count (ANC) was $< 1.5 \times 10^9/l$ and/or platelet count was $< 100 \times 10^9/l$. If ANC on day 8 was $< 1.5 \times 10^9/l$ and/or platelet count was $< 50 \times 10^9/l$, day 8 treatment was cancelled. Dose reductions were performed in patients who had grade 4 neutropenia or grade 3 thrombocytopenia lasting more than 7 days and in case of febrile neutropenia ($\geq 38.5^\circ C$) associated or not with documented infection. Furthermore, dose reduction should be considered by investigator in case of non-hematologic toxicities grade 3-4 except alopecia and peripheral neuropathy. For peripheral neuropathy, paclitaxel was reduced for grade 2 and was discontinued for grade 3. The following dose modifications schemes were used: paclitaxel: dose level -1; 70 mg/m²; dose level -2: 60 mg/m². For gemcitabine the dose was reduced to 66% if proteinuria or hematuria CTC grade II was observed. In that case, chrome-EDTA clearance (GFR) should be done every 6 weeks. If GFR was moderately low gemcitabine was to be reduced to 50%. If

Table 1: Characteristics for patients with metastatic breast cancer receiving paclitaxel and gemcitabine.

Characteristics	
Number	42
Age, years (median, range)	56.5 (33-72)
Performance status	
0	14 (33.3%)
1	20 (47.6%)
2	6 (14.3%)
Not known	2 (4.8%)
No. of metastatic sites (median, range)	2 (1-5)
Type of metastatic site	
Soft tissue	7 (16.7%)
Lung	20 (47.6%)
Pleura	8 (19.0%)
Liver	22 (52.4%)
Bone	25 (59.5%)
Lymph nodes	20 (47.6%)
Other	7 (16.7%)
Hormone receptor status	
Estrogen/progesterone positive	23 (54.8%)
Receptor negative	15 (35.7%)
Unknown	4 (9.5%)
Prior chemotherapy	
Adjuvant	
CMF	12 (28.6%)
CEF	8 (19.0%)
Other	3 (7.2%)
None	19 (45.2%)
Metastatic disease	
Epirubicin	30 (71.4%)
Other	3 (7.2%)
None	9 (21.4%)
Prior hormonal therapy adjuvant	
Yes	13 (31.0%)
No	28 (66.7%)
Unknown/missing	1 (2.3%)
Prior hormonal therapy for metastatic disease	
Yes	20 (47.6%)
No	22 (52.4%)
Time from diagnosis to metastatic disease, months (median, range)	31.4 (0-171.5)

CEF = cyclophosphamide, epirubicin and 5-fluorouracil

CMF = cyclophosphamide, methotrexate and 5-fluorouracil

serum creatinine ≥ 1.5 UNL, gemcitabine was reduced to 50% and if further increase gemcitabine should be stopped.

Statistical methods

The primary objective of this study was to evaluate response. Secondary objectives were TTP, OS and toxicity. We also estimated the clinical benefit rate (CBR). RR was defined as the sum of complete response (CR) and partial response (PR) according to RECIST 1.0 criteria divided by the number of patients feasible for evaluation [18]. CBR was defined as the sum of CR, PR and stable disease ≥ 6 months ($SD \geq 6$ months), divided by the sum of patients feasible for evaluation. The 95% confidence intervals (CI) were calculated. Time to event end-points, (TTP and OS), were evaluated using the Kaplan-Meier method. TTP was defined as the date of first infusion of paclitaxel/gemcitabine to progression was observed or to cancer related death. OS was defined as the day of the first infusion to death. Toxicity, treatment and patient characteristics were summarized using descriptive statistics.

Number of patients in the study is based on a two-stage phase II design. Intention-to-treat analysis was performed. By using a significance level of 0.05 ($\alpha=0.05$) and a power of 80% ($\beta = 0.20$), 14

patients should be included in the first step in order to find a true RR of at least 20%. Further inclusion ceases if less than 1/14 patients show a clinical response. If 1 or more showed a clinical response, 40 patients should be included.

Results

Patient characteristics

Forty-two patients were enrolled in the period between May 2001 and October 2004. Median age was 56.5 years (range 33-72 years). Fourteen patients (33.3%) had performance status (PS) 0, twenty patients (47.6%) had PS 1 and six patients (14.3%) had PS 2. For two patients (4.8%), the PS was not known. The median number of metastatic sites was 2 (range 1-5) and the main metastatic sites included lung (47.6%), liver (53.4%) and bones (59.5%) (Table 1).

Forty-two were evaluable for toxicity, OS and TTP. Forty patients were evaluable for response. Two patients were excluded, one stopped because of an allergic reaction to the study drug during first treatment, and one went off-study after one cycle because of patient's request, and was not evaluated. Twenty-three patients (54.8%) had received adjuvant chemotherapy eight of them (19.0%) had epirubicin in the adjuvant setting. Thirty-three patients (78.6%) had received one regime of chemotherapy in the metastatic setting, of whom thirty patients (71.4%) had epirubicin.

Efficacy

No patients achieved CR. Ten (23.8%) achieved PR, yielding an objective RR of 25% [95% confidence interval (CI) 12.7-41.2%]. A total of twenty-four patients (57.1%) had SD, and six (14.3%) had progressive disease. Nine patients had SD ≥ 6 months, yielding a CBR of 47.5% (95% CI, 31.5-63.9%). Median TTP for the entire population was 4.9 months (95% CI, 3.2-6.5 months). The median OS was 10.6 months (95% CI, 8.3-12.9 months) (Table 2).

Toxicity

One-hundred sixty-two adverse events (AE) were reported (CTC grade 2-4). Most AE's were CTC grade 2. Six reported AE's were grade 4; all of them were hematologic (one febrile neutropenia). No toxicity-related deaths were observed. Hematologic toxicity comprised the most frequent treatment-emergent side effect. CTC grade 3 and 4 neutropenia, leucopenia, thrombocytopenia and anemia were seen in seventeen (40.5%), six (14.3%), three (7.1%) and one (2.4%) patients, respectively. Nine patients (21.4%) experienced

Table 2: Efficacy in patients with metastatic breast cancer receiving paclitaxel and gemcitabine.

Response (RECIST 1.0) N = 40	No (%)	
Complete response (CR)	0 (0 %)	
Partial response (PR)	10 (23.8 %)	
Stable disease (SD)	24(57.1 %)	
Progressive disease (PD)	6 (14.3 %)	
Not evaluable(NE)	2 (4.8 %)	
n = 42		
	Median (range)	95% confidence interval
TTP (Months)	4.9 (0.3-15.9)	(3.2-6.5)
OS (Months)	10.6 (1.0-45.4)	(8.3-12.9)

Table 3: Drug related toxicity in patients with metastatic breast cancer receiving paclitaxel and gemcitabine.

Toxicity N=42	Grade 2 No. (%)	Grade 3 No. (%)	Grade 4 No. (%)
Hematologic			
Neutropenia	5 (11.9%)	13 (31.0%)	4 (9.5%)
Leucopenia	4 (9.5%)	6 (14.3%)	0 (0 %)
Trombocytopenia	3 (7.1%)	2 (4.8%)	1 (2.4%)
Anemia	2 (4.8%)	1 (2.4%)	0 (0%)
Febrile neutropenia	0 (0 %)	0 (0 %)	1 (2.4%)
Non hematologic			
Neurotoxicity	6 (14.3%)	3 (7.1%)	0 (0 %)
Myalgia/atralgia	9 (21.4%)	2 (4.8%)	0 (0 %)
Nausea/vomiting	10 (23.8%)	0 (0 %)	0 (0 %)
Diarrhea	3 (7.1%)	2 (4.8%)	0 (0 %)
Constipation	6 (14.3%)	1 (2.4%)	0 (0 %)
Oedema	7 (16.7%)	1 (2.4%)	0 (0 %)
Fever	4 (9.5%)	0 (0 %)	0 (0 %)
Rash	2 (4.8%)	1 (2.4%)	0 (0 %)
Allergic reaction	1 (2.4%)	2 (4.8%)	0 (0 %)
Infection	1 (2.4%)	1 (2.4%)	0 (0 %)
Fatigue	16 (38.1%)	2 (4.8%)	0 (0 %)
Other	32 (76.2%)	8 (19.0%)	0 (0 %)

NCI CTC National Cancer Institute Common Toxicity Criteria version 2
 *) "other" grade 3 AE's included: back pain, bronchospasm, dyspnoea, hypomagnesaemia, hyponatremia and stomach pain.

neurotoxicity CTC grade 2 and 3. Two patients went off-study because of study drug toxicity. One because off an allergic reaction and one because of cumulative hematologic toxicity (Table 3).

Dose intensity

For paclitaxel 30 patients (71.4%) received >75% of the possible dosemax. Ten patients (23.8%) received between 50% and 75% of dosemax, and two patients (4.8%) received less than 50% of dosemax. For gemcitabine 30 patients (71.4%) received >75% of dosemax, nine patients (21.4%) received between 50% and 75% of dosemax and three patients (7.2%) received less than 50% of dosemax.

Discussion

The purpose of this study was to evaluate the efficacy and toxicity of a split-dose paclitaxel regimen in combination with gemcitabine. The RR in 40 patients was 25% with no patients achieving CR. Ten patients (25%) achieved PR and twenty-three patients (54.8%) had SD and the CBR was 47.5%. Median TTP was 4.9 months and median OS was 10.6 months. The toxicity profile was favorable, and treatment was well tolerated.

The combination of paclitaxel and gemcitabine has been studied in several phase II studies and in randomized phase III studies showing RRs of 40%-67% [19-25]. The schedules used in these studies were mostly 3-weeks schedules with paclitaxel 175 mg/m² on day 1, and gemcitabine 1000-1250 mg/m² on day 1 and 8 [19-21,24]. One randomized phase II study [23] compared the split dose paclitaxel schedule (paclitaxel 100 mg/m² days 1 and 8, gemcitabine 1000 mg/

m² days 1 and 8, repeated every 3 weeks) with the 3-week schedule. This showed similar efficacy and toxicity between schedules, but the study was an Asian study with primarily Asian patients, and given the possible differences in enzymatic activity in regards to race, it could be different in a Caucasian population. Furthermore, a weekly administration of paclitaxel monotherapy was compared to 3-week schedule in the randomized phase III study by Seidman, et al. [13]. It showed RRs of 42% versus 29% in favor of weekly administration. This makes the split-dose schedule of the present study interesting in matters of efficacy and toxicity.

The RR in the present study was lower compared to prior studies [19-25]. A direct comparison of response from one trial to another is of course difficult given the different patient characteristics and different schedules. The majority of patients in the present study (78.6%) had already been exposed to chemotherapy in the metastatic setting, and this was generally not the case in the prior studies, although two phase II studies of heavily pre-treated patients showed RRs of 55 and 53%, respectively [19, 22]. When comparing with the split-dose paclitaxel regimen in the randomized phase II study by Khoo, et al. [23], which was comparable to the present study regarding schedule, we also demonstrated a lower RR in the present study; 25% versus 52.2%. This difference can to some extent be explained by the lower amount of pre-treated patients in this study. In the prior studies median TTP was in the range of 6.1-11 months [20-25] and OS in the range of 12-25.7 months [19-24] with no obvious correlation between the shortest time and amount of pre-treated patients.

The toxicity in the present study is comparable to the randomized trials [21,23,24] with no obvious advantages in the split-dose schedule. We did see lower grade 4 neutropenia in the present study, but the amount of febrile neutropenia and neurotoxicity were about the same.

When comparing the present study to prior studies on paclitaxel monotherapy [7-13] the combination did not provide any new evidence of a benefit in combining with gemcitabine in regards to efficacy.

The optimal treatment strategy for MBC is an ongoing discussion. Questions regarding sequential versus combination remains unanswered. The combinations of taxanes with other chemotherapies have been of interest for long. The combination of docetaxel and gemcitabine failed in the randomized phase III study of Nielsen, et al. [26] to proof any benefit. The combination of docetaxel and capecitabine was evaluated in the phase III trial by O'Shaughnessy, et al. [27]. It showed superior OS, TTP and RR in favor of the combination, with an RR of 41.1% vs. 26.2%, but because of additional toxicity and because it has not been compared to sequential therapy, the combination is rarely used [28]. In spite of this, it is to some extent still believed that a subgroup of patients could benefit from it. This could possibly be the case for patients with an extensive amount of visceral disease who may take advantage from the greater tumor response [28].

Conclusion

In conclusion, this phase II study showed RR, TTP and OS that

was lower when compared to other studies even studies of heavily pre-treated patients. This present study was comparable in toxicity to other studies and is maybe comparable in efficacy, but it did not bring any reason to believe a further benefit in neither efficacy nor toxicity could be achieved in the combination by splitting the paclitaxel into two doses.

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Author Contribution

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Final approval of manuscript: All

References

1. Ferlay J, Soerjomataram I, Dikshit R, Eser S, Mathers C, Rebelo M, et al. Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*. 2015; 136: E359-386.
2. Brewster AM, Hortobagyi GN, Broglio KR, Kau SW, Santa-Maria CA, Arun B, et al. Residual risk of breast cancer recurrence 5 years after adjuvant therapy. *J Natl Cancer Inst*. 2008; 100: 1179-1183.
3. Wilcken N, Dear R. Chemotherapy in metastatic breast cancer: A summary of all randomised trials reported 2000-2007. *Eur J Cancer*. 2008; 44: 2218-2225.
4. Burstein HJ, Harris JR, Morrow M: Malignant tumors of the breast, in DeVita Jr, Hellman S, Rosenberg SA (eds): *Cancer: Principles and practice of oncology* 9th ed. Lippencott: Williams & Wilkins; 2011. 1401-1446.
5. Jensen PB, Holm B, Sorensen M, Christensen IJ, Sehested M. In vitro cross-resistance and collateral sensitivity in seven resistant small-cell lung cancer cell lines: preclinical identification of suitable drug partners to taxotere, taxol, topotecan and gemcitabine. *Br J Cancer*. 1997; 75: 869-877.
6. Gazitt Y, Rothenberg ML, Hilsenbeck SG, Fey V, Thomas C, Montgomery W. Bcl-2 over expression is associated with resistance to paclitaxel, but not gemcitabine. *Int J Oncol* 1998; 13: 839-848.
7. Abrams JS, Vena DA, Baltz J, Adams J, Montello M, Christian M, et al. Paclitaxel activity in heavily pretreated breast cancer: a National Cancer Institute Treatment Referral Center trial. *J Clin Oncol*. 1995; 13: 2056-2065.
8. Nabholz JM, Gelmon K, Bontenbal M, Spielmann M, Catimel G, Conte P et al. Multicenter, randomized comparative study of two doses of paclitaxel in patients with metastatic breast cancer. *J Clin Oncol*. 1996; 14: 1858-1867.
9. Seidman AD, Hudis CA, Albanell J, Tong W, Tepler I, Currie V, et al. Dose-dense therapy with weekly 1-hour paclitaxel infusions in the treatment of metastatic breast cancer. *J Clin Oncol*. 1998; 16: 3353-3361.
10. Perez EA, Vogel CL, Irwin DH, Kirshner JJ, Patel R. Multicenter phase II trial of weekly paclitaxel in women with metastatic breast cancer. *J Clin Oncol*. 2001; 19: 4216-4223.
11. Gori S, Mosconi AM, Basurtol C, Cherubini R, De Angelis V, Tonato M, et al. Weekly paclitaxel in metastatic breast cancer patients: a phase II study. *Tumori*. 2002; 88: 470-473.

12. Lombardi D, Crivellari D, Scuderi C, Magri MD, Spazzapan S, Sorio R, et al. Long-term, weekly one-hour infusion of paclitaxel in patients with metastatic breast cancer: a phase II monoinstitutional study. *Tumori*. 2004; 90: 285-288.
13. Seidman AD, Berry D, Cirrincione C, Harris L, Muss H, Marcom PK, et al. Randomized phase III trial of weekly compared with every-3-weeks paclitaxel for metastatic breast cancer, with trastuzumab for all HER-2 overexpressors and random assignment to trastuzumab or not in HER-2 nonoverexpressors: final results of Cancer and Leukemia Group B protocol 9840. *J Clin Oncol*. 2008; 26: 1642-1649.
14. Carmichael J, Possinger K, Phillip P, Beykirch M, Kerr H, Walling J, et al. Advanced breast cancer: a phase II trial with gemcitabine. *J Clin Oncol*. 1995; 13: 2731-2736.
15. Blackstein M, Vogel CL, Ambinder R, Cowan J, Iglesias J, Melemed A. Gemcitabine as first-line therapy in patients with metastatic breast cancer: a phase II trial. *Oncology*. 2002; 62: 2-8.
16. Modi S, Currie VE, Seidman AD, Back AM, Panagea KS, Theodoulou M, et al. A phase II trial of gemcitabine in patients with metastatic breast cancer previously treated with an anthracycline and taxane. *Clin Breast Cancer*. 2005; 6: 55-60.
17. Possinger K, Kaufmann M, Coleman R, Stuart NS, Helsing M, Ohnmacht U, et al. Phase II study of gemcitabine as first-line chemotherapy in patients with advanced or metastatic breast cancer. *Anticancer Drugs*. 1999; 10: 155-162.
18. Therasse P, Arbutk SG, Eisenhauer EA, Wanders J, Kaplan RS, Rubinstein L, et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J Natl Cancer Inst*. 2000; 92: 205-216.
19. Murad AM. Paclitaxel and gemcitabine as salvage treatment in metastatic breast cancer. *Oncology*. 2003; 17: 26-32.
20. Delfino C, Caccia G, Gonzáles LR, Mickiewicz E, Rodger J, Balbiani L, et al. Gemcitabine plus paclitaxel as first-line chemotherapy for patients with advanced breast cancer. *Oncology*. 2004; 66: 18-23.
21. Allouache D, Gawande SR, Tubiana-Hulin M, Tubiana-Mathieu N, Piperno-Neumann S, Mefti F, et al. First-line therapy with gemcitabine and paclitaxel in locally, recurrent or metastatic breast cancer: a phase II study. *BMC Cancer*. 2005; 5: 151.
22. Vici P, Capomolla E, Foggi P, Carpano S, Conti F, Paoletti G, et al. High activity of salvage treatment with biweekly paclitaxel-gemcitabine combination in heavily pretreated breast cancer patients. *J Exp Clin Cancer Res*. 2006; 25: 39-44.
23. Khoo KS, Manzoor Zaidi SH, Srimuninnimit V, Song S, Nair R, Ngelangel CA, et al. Gemcitabine and split-dose paclitaxel or docetaxel in metastatic breast cancer: a randomised phase II study. *Eur J Cancer*. 2006; 42: 1797-1806.
24. Albain KS, Nag SM, Calderillo-Ruiz G, Jordaan JP, Llombart AC, Pluzanska A et al. Gemcitabine plus paclitaxel versus paclitaxel monotherapy in patients with metastatic breast cancer and prior anthracycline treatment. *J Clin Oncol*. 2008; 26: 3950-3957.
25. Del Mastro L, Fabi A, Mansutti M, De Laurentiis M, Durando A, Merlo DF, et al. 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*. 2013; 13: 164.
26. Nielsen DL, Bjerre KD, Jakobsen EH, Cold S, Stenbygaard L, Sørensen PG, et al. Gemcitabine plus docetaxel versus docetaxel in patients with predominantly human epidermal growth factor receptor 2-negative locally advanced or metastatic breast cancer: a randomized, phase III study by the Danish Breast Cancer Cooperative Group. *J Clin Oncol*. 2011; 29: 4748-4754.
27. O'Shaughnessy J, Miles D, Vukelja S, Moiseyenko V, Ayoub JP, Cervantes G et al. Superior survival with capecitabine plus docetaxel combination therapy in anthracycline pre-treated patients with advanced breast cancer: phase III trial results. *J Clin Oncol*. 2002; 20: 2812-2823.
28. Cardoso F, Costa A, Norton L, Senkus E, Aapro M, Andre F, et al. ESO-ESMO 2nd international consensus guidelines for advanced breast cancer (ABC2). *Ann Oncol*. 2014; 23: 489-502.