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ORIGINAL ARTICLE

Combination versus sequential paclitaxel plus gemcitabine as first-line chemotherapy for women with metastatic breast cancer: a prospective randomized phase II study

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Summary

Purpose: *Paclitaxel (T) plus gemcitabine (G) is an active concomitant combination for the treatment of metastatic breast cancer (MBC). However, the efficacy of sequential administration of these two drugs is unclear. This randomized phase II study was conducted to evaluate the efficacy of T and G administered either as a concomitant or as a sequential regimen in patients with MBC.*

Methods: *Patients with MBC (n=66) were randomized to either receive 6 cycles of concomitant T and G or 4 cycles of T followed by 4 cycles of G, as first line chemotherapy. With no progression, the arms would switch to maintenance with paclitaxel. Progression free survival (PFS) was defined as the primary endpoint; secondary endpoints were the overall response rate (ORR), overall survival (OS), and toxicity. In total, 33 patients were randomized to the concomitant or sequential arms. Patient characteristics were well balanced. The median number of chemotherapy cycles was 6 for the concomitant arm and 8 for the sequential arm.*

Results: *No significant difference was observed in terms of PFS, ORR, and OS. Only 13 (39.4%) patients progressed in the sequential arm. Although there was no significant difference between the two arms (p=0.056),the sequential arm had a remarkable trend of longer PFS than the concomitant arm. Toxicities were manageable and similar in both arms. The incidence of neutropenia was significantly higher in the concomitant arm (90.9%) than in the sequential arm (60.6%). Grade 3 or 4 neutropenia was not significantly different between the two arms.*

Conclusions: *Concomitant and sequential treatment with paclitaxel and gemcitabine had no significant difference in terms of PFS.*

Key words: *concomitant, gemcitabine, metastatic breast cancer, paclitaxel, sequential*

Introduction

Breast cancer is one of the most prevalent cancers in the world and causes approximately half a million deaths per year worldwide [1].Metastatic breast cancer (MBC) is generally incurable, with a median survival time of 2-3 years, and is the main cause of death. Fortunately, MBC is very effectively treated with chemotherapy, endocrine therapy, and targeted therapies. Nowadays, improving survival and quality of life is a major therapeutic goal [2].

Chemotherapy plays an important role in the treatment of MBCs. However, the optimal combination, sequence,and timing of systemic agents for MBC remain unresolved. Few appropriately

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powered randomized clinical trials have addressed the question of sequential use of single cytotoxic agents versus upfront combination chemotherapy for MBC. Selection of treatment is based on the consideration of the site of recurrence, symptoms, anticipated response to treatment, expected toxicities, quality of life, and patient preference. Combination chemotherapy is often administered to obtain a response in immediately life-threatening circumstances, whereas sequential monotherapy is considered for less urgent treatment needs.

Dear et al. [3] compared combination chemotherapy with sequential single agents in women with metastatic breast cancer. The results showed there was no difference in OS between the combination arm and the sequential arm with an overall hazard ratio (HR) of 1.04 (95% confidence interval [CI] 0.93 to 1.16; p=0.45). There was weak evidence of a higher risk of progression in the combination arm (HR 1.11; 95% CI 0.99 to 1.25; p=0.08). Overall tumour response rates were higher in the combination arm (relative risk [RR] 1.16; 95% CI 1.06 to 1.28; p=0.001). In the subgroup analysis, the trials used a schema in which chemotherapy was given for a set number of cycles in the sequential arm. Most of the regimens of the trials enrolled in this meta-analysis were traditional drugs, such as anthracyclines and taxanes, not modern drugs. The combination of paclitaxel and gemcitabine demonstrated consistently high response rates (40-71%) and manageable toxicity as a first-line or salvage therapy in patients with advanced breast cancer [4-6].

Albain et al. [7] randomly assigned 529 women, whose MBC had been treated with anthracyclines, to the combination of 3-weekly paclitaxel and gemcitabine (GP) or paclitaxel monotherapy. In this study, RR, time to progression (TTP), and OS were improved by the addition of gemcitabine to paclitaxel. The delivery of additional chemotherapy following progression was similar between the 2 groups, but only 15.6% of patients in the paclitaxel monotherapy group crossed over to gemcitabine. No data comparing GP with paclitaxel followed by gemcitabine (P → G) are available. In a smaller study, 100 patients with MBC were randomly assigned to eight cycles of combination gemcitabine and docetaxel (GT) or four sequential cycles of docetaxel followed by 4 cycles of gemcitabine (T→G). No difference in RR, TTP, and OS was observed [8].Single agent paclitaxelyielded response rates of 21% to 49% after prior anthracycline therapy [9,10]. Overall response rates of 14% to 42% were reported for gemcitabine treatment, usually after administration of both anthracyclines and taxanes [11-13].

The primary goal of the current study was to determine whether the sequential regimen of paclitaxel and gemcitabine yielded better PFS than the standard concomitant regimen. Secondary aims were to confirm a lower toxicity in the sequential arm and to compare the two regimens with regard to response rate,OS, and toxicity profile.

Methods

Eligibility criteria

The study was designed as a phase II, randomized, open label, and prospective, single centre clinical trial. Patient recruitment began in October 2014 and concluded in December 2015. All patients provided written informed consent.The trial was conducted in accordance with the Declaration of Helsinki and was approved by the ethics committee of Peking University Cancer Hospital. The trial was registered on Oct. 17, 2014, with a registration number ChiCTR-IPR-14005583 (http://www.chictr.org.cn/index.aspx).

The main eligibility criteria included women aged ≥18 years with histologically confirmed MBC (adjuvant chemotherapy with paclitaxel, DFS longer than 1 year), measurable disease, Eastern Cooperative Oncology Group performance status ≤2, and normal bone marrow, renal, or hepatic function. Baseline laboratory study requirements included leukocytes >3×10^9/L, neutrophils >1.5×10^9/L, platelets >100×10^9/L, haemoglobin>10 g/dL, as well as adequate liver and renal function (bilirubin ≤1.5 times the upper limit of normal [ULN]; alanine transaminase [ALT] and aspartate transaminase [AST]

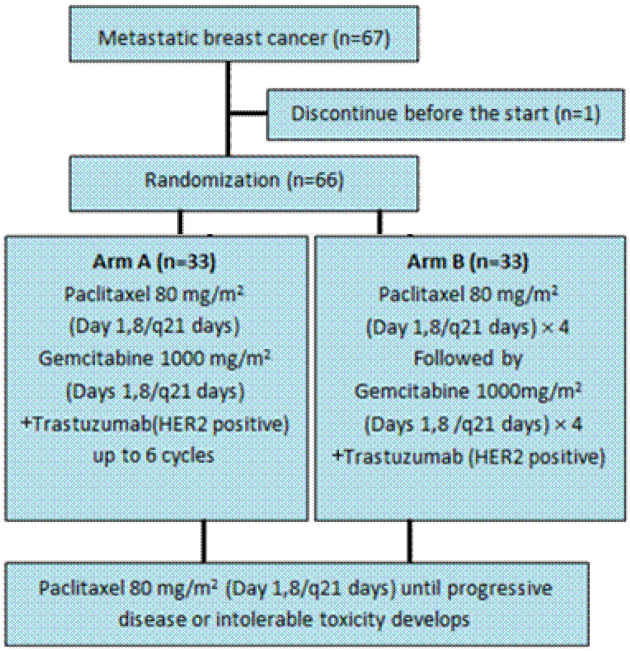

Figure 1. Trial design. Arm A consists of concomitant treatment with 6 cycles of paclitaxel and gemcitabine. Arm B consists of sequential treatment with 4 cycles of paclitaxel followed by 4 cycles of gemcitabine. Then both Arm A and Arm B switch to maintenance with paclitaxel.

≤2 times the ULN; creatinine ≤1.5 times the ULN). Normal cardiac function was confirmed by left ventricular ejection fraction (LVEF) ≥50%.

Patients were excluded from the study if they had received prior chemotherapy or radiotherapy for metastatic disease. However, patients with previous neoadjuvant or adjuvant chemotherapy were included, provided that the treatment had been completed at least 12 months before the study initiation. Patients with hormone therapy in the adjuvant and/or metastatic setting were included with the latter only allowed if the patient showed progressive disease at study initiation. Further exclusion criteria included a history of malignancy other than breast cancer; however, patients with nonmelanoma skin cancer, *in situ* cervical carcinoma, or other cancer with no evidence of disease for more than 5 years were eligible. Patients were also excluded if they had known metastatic disease involving the central nervous system, pre-existing motor or sensory neurotoxicity more than grade 2, or a history of other serious illnesses (e.g. congestive heart failure, angina pectoris, AIDS), uncontrolled infection, if they showed contraindication for corticosteroid use, or were pregnant or lactating.

Chemotherapy regimen

Patients were randomly assigned to either of the two treatment arms (Figure 1). Arm A (concomitant arm) included paclitaxel (80 mg/m^2) plus gemcitabine (1000 mg/m^2) administered intravenously for 6 cycles. Arm B (sequential arm) included 4 cycles of paclitaxel (80 mg/m^2) followed by 4 cycles of gemcitabine (1000 mg/m^2). HER2 positive patients received trastuzumab. Subsequently, the paclitaxel treatment was continued until objective disease progression was documented or other events that required discontinuation occurred. At this time, patient participation in the study was terminated and further therapy was initiated at the discretion of the treating physician.

Dose modifications were planned for severe toxicity. Patients who experienced febrile neutropenia (<0.5×10^9/L and >38.1°C body temperature) and required antibiotics and/or hospitalization had a 20% dose reduction for both drugs. Blood cell counts were measured twice a week until recovery. After a second episode of febrile neutropenia, the patients were withdrawn from the study. Both drug doses were also reduced by 20% in the event of grade 3 mucositis or grade ≥ 2 skin toxicity and after a second episode of either, the patients were withdrawn from the study.

Response evaluation

OS was calculated from the date of randomization to the date of death or last follow-up. PFS was calculated from the date of randomization to documented progressive disease (PD) or death. Re-evaluation of patient tumour status was performed in both arms every other cycle and in two-month intervals thereafter. Response was assessed using RECIST criteria. Complete response (CR) was defined as the disappearance of all measurable lesions for a minimum of eight weeks. Partial response (PR) was defined as 30% or more reduction in the sum of the longest diameters of target lesions, no increase of lesion size, and no new lesions. Stable disease (SD) was defined as less than 30% decrease and less than 20% increase without the appearance of new lesions. PD was defined as at least a 20% increase in tumour size or the appearance of new lesions.

Safety

Toxicity was assessed at the end of each cycle according to the National Cancer Institute-Common Toxicity Criteria (NCI-CTC), version 3.0.All patients who received at least 1 dose of gemcitabine or docetaxel were evaluable for safety analysis. All patients with a minimum of one response assessment were also evaluable for efficacy.

Statistics

All statistics were calculated using statistical package for the social sciences (SPSS) 18.0 software. Log-rank tests and Kaplan-Meier estimations were performed for PFS and OS. Chi square test or Fisher's exact test were used to compare response rates or toxicities in both treatment arms. Differences were assumed to be significant when $p<0.05$.

Results

Patient characteristics

67 women were recruited and randomly assigned to Arm A (n=34) or Arm B (n=33). One patient decided to withdraw from the trial before the start of treatment. A total of 66patients were evaluable for safety (99%) and 63 for efficacy (98%). Approximately half the patients completed treatment in both arms (60.6% Arm A vs 57.6 % Arm B), and one third of the patients switched to paclitaxel maintenance therapy (39.4% Arm A vs 36.4% Arm B). The main reasons for treatment discontinuation included disease progression (20.0% vs 15.8%), adverse events (5.0% vs 0%), and patients' wishes (75% vs 84.2%) (Table 1).

Baseline characteristics and demographics are listed in Table 2. The median age was 55 years (range 32-73). More than half of the patients had visceral involvement, and more than one third of the patients had three or more metastatic sites. Arm A had more oestrogen receptor positive patients than Arm B (75.8% and 51.5%, respectively; p=0.041) and less HER2 positive patients than Arm B (9.1% and 30.3%, respectively; p=0.025). The 3 patients positive for HER2 in Arm A received treatment with trastuzumab, while only 8 of 10 HER2 positive patients in Arm B received trastuzumab.

Antitumour activity

According to intent-to-treat analysis, the overall response rate was 36.3% with the combi-

nation treatment and 42.4% with the sequential regimen (Table 3). At a median follow-up of 10.7 months, PFS was 8.3 months (95% CI 4.4-12.3) for the combination. There were only 13 (39.4%) cases that progressed in the sequential arm. Although there was no significant difference between the two arms (p=0.056), the sequential arm strongly trended toward longer PFS than the combination arm (Figure 2). Since there were more HER2 negative patients in Arm A than in Arm B (87.9% and 63.6%, respectively; p=0.025), we analysed the PFS of HER2 negative subgroup and found that the PFS of Arm B had significantly longer PFS than Arm A (8.3 months, 95% CI:5.9-10.8 months) (p=0.032; Figure 3). The median PFS of patients who did not receive maintenance therapy in the combination arm (n=20) and the sequential arm (n=21) was 7.7 months (95% CI 6.1-9.3) and 16.6 months (95% CI 5.9-27.4), respectively, but these PFS were not significantly different (p=0.197;Figure 4). A total of 7 patients died until the last follow up period. The estimated OS probabilities were 93.6% at 1 year and 82.2% at 2 years.

Safety

All patients who received at least one dose were assessed for safety (n=66). A dose reduction was performed in 8 (24.2%) patients in the concomitant arm and in 4 (12.1%) who received sequential therapy (p=0.202). Dose delays were necessary in 12 (36.4%) patients receiving TG, and 9 (27.6%) on T → G (p=0.428;Table 4).

Table 1. Treatment administration

Characteristics	*Arm A (n=33)*	*Arm B (n=33)*
Chemotherapy cycles		
Total N	192	244
Median	6	8
Range	1-12	1-20
Treatment completed, n (%)	20 (60.6)	19 (57.6)
Maintenance cycles		
Total N	40	37
Median	2	2.5
Range	2-4	1-8
Early study withdrawal reasons, n (%) (Arm A < 6 cycles, Arm B < 8 cycles)		
Disease progression	3 (23.1)	2 (14.3)
Patient's decision	8 (61.5)	12 (85.7)
Adverse events	2 (15.4)	
Study discontinuation reasons, n (%)	20	19
Disease progression	4 (20.0)	3 (15.8)
Patient's decision	15 (75.0)	16 (84.2)
Adverse events	1 (5.0)	

Table 2. Clinicopathological characteristics of the metastatic breast cancer patients

Characteristics	*Arm A, n=33 n (%)*	*Arm B, n=33 n (%)*
Age (years)		
Median (range)	53 (36-67)	57 (32-73)
Histology		
IDC	30 (90.9)	32 (97.0)
ILC	2 (6.1)	0 (0.0)
Others	1 (3.0)	1 (3.0)
Stage of disease at time of diagnosis		
Stage I	3 (9.1)	8 (24.2)
Stage II	13 (39.4)	11 (33.3)
Stage III	15 (45.5)	6 (18.2)
Stage IV	1 (3.0)	7 (21.2)
Unknown	1 (3.0)	1 (3)
Oestrogen receptor		
Negative	8 (24.2)	16 (48.5)
Positive	25 (75.8)	17 (51.5)
Progesterone receptor		
Negative	11 (33.3)	15 (45.5)
Positive	21 (63.6)	17 (51.5)
Unknown	1 (3.0)	1 (3.0)
HER2 status		
Negative	29 (87.9)	21 (63.6)
Positive	3 (9.1)	10 (30.3)
Unknown	1 (3.0)	2 (6.1)
Ki-67		
Low expression (<20%)	15 (45.5)	20 (60.6)
High expression (≥20%)	17 (55.5)	12 (36.4)
Unknown	1 (3.0)	1 (3.0)
Localization of metastasis		
Liver metastasis	8 (24.2)	8 (24.2)
Lung metastasis	12 (36.4)	12 (36.4)
Brain metastasis	1 (3.0)	2 (6.1)
Bone metastasis	16 (48.5)	20 (60.6)
Lymph nodes metastasis	16 (48.5)	21 (63.6)
Visceral metastasis (liver, lung, brain)	18 (54.5)	17 (51.5)
More than 3 sites of metastasis	10 (30.3)	12 (36.4)
DFS months (range)	4.6 (0.3-15.7)	4.0 (0.9-14.2)

Table 3. Therapeutic effects

Clinical response	*Arm A n (%)*	*Arm B n (%)*
CR	1 (3.0)	1 (3.0)
PR	11 (33.3)	13 (39.4)
SD	17 (51.5)	15 (45.5)
PD	3 (9.1)	2 (6.1)
ORR(CR+PR)	12 (36.4)	14 (45.2)
PFS(mos)	8.3 (95% CI 4.4-12.3)	

The incidence of neutropenia was significantly higher in the concomitant arm (90.9%) than in the sequential arm (60.6%), while grade 3 or 4 neutropenia had no significant difference between the two arms. The overall incidence of anaemia and thrombocytopenia was similar in both arms. The non-haematological adverse events were comparable between the two arms. The concomitant arm had a higher incidence of fatigue (75.8% vs 39.4%, p=0.003) and a lower incidence of sensory neuropathy (38.5% 0vs 64.5%, p=0.05).

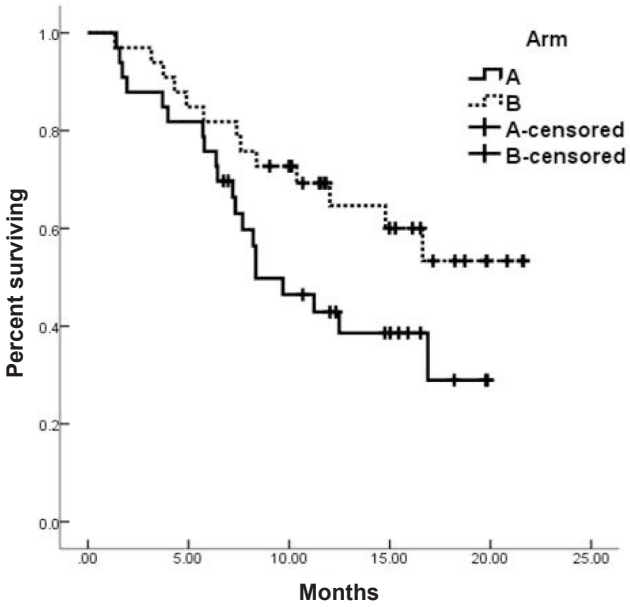

Figure 2. Progression-free survival (p=0.056).

Discussion

The optimal treatment approach in MBC, whether anti-tumour agents are administered sequentially or in combination, remains controversial. Dear et al. [3] reported in the Cochrane review that there was weak evidence of a higher TTP benefit in the sequential arm. In the subgroup analysis, the trials that used a pre-planned sequential design had no difference in PFS compared to the combination arm.

Our prospective randomized trial demonstrated that there was no difference between the concomitant combination of paclitaxel and gemcitabine and sequential treatment in terms of PFS, ORR, and OS. However, the sequential arm had a clear trend of longer PFS. However, the combination arm was also associated with a significantly higher incidence of grade 3 or 4 neutropenia.

Concomitant TG in our trial yielded a median PFS of 8.4 months. This result compared well with data of previous reports. One previous report [14] was a phase III trial comparing the efficacy of paclitaxel plus gemcitabine (TG) versus paclitaxel in patients with advanced breast cancer. The TG combination was administered as 1,250 mg/m^2 gemcitabine on days 1 and 8 plus 175 mg/m^2 paclitaxel on day 1, which was higher than in our study. Median TTP on TG was 6.14 months, which was significantly better than paclitaxel (p=0.0002). Xu Bingheet al. [15] reported a phase II selection trial, which compared the objective tumour response of biweekly gemcitabine/paclitaxel, gemcitabine/carboplatin,

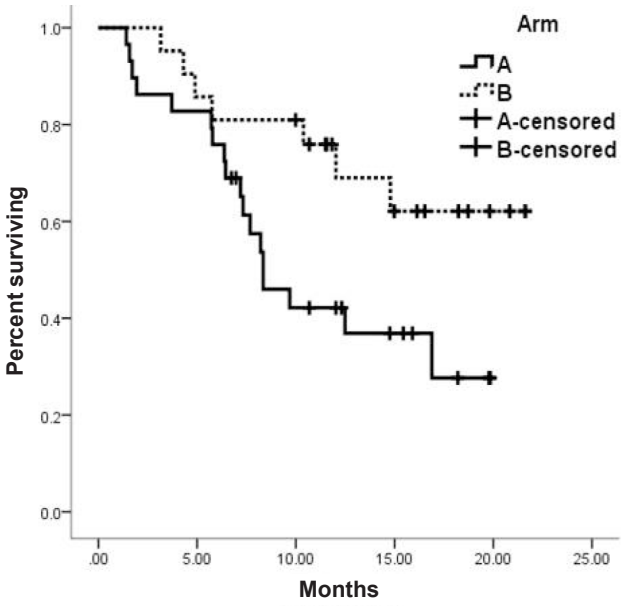

Figure 3. Progression-free survival of patients with HER2 negative tumors (p=0.032).

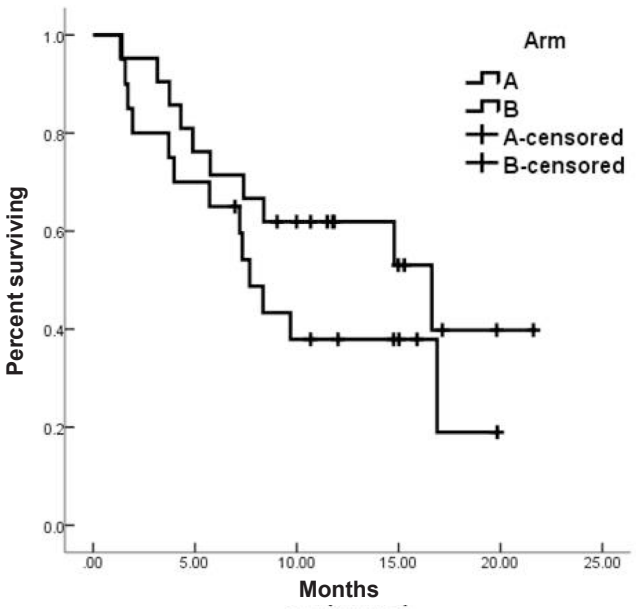

Figure 4. Progression-free survival of patients with no maintenance therapy (p=0.197).

Table 4. Drug-related common toxicities

Toxicity	*Grade*	*Arm A*				*Arm B*			
		1 *n (%)*	*2* *n (%)*	*3* *n (%)*	*4* *n (%)*	*1* *n (%)*	*2* *n (%)*	*3* *n (%)*	*4* *n (%)*
Haematological									
	Neutropenia	8 (24.2)	12 (36.4)	8 (24.2)	2 (6.1)	8 (24.2)	6 (18.2)	6 (18.2)	0 (0.0)
	Anaemia	6 (18.2)	4 (12.1)	1 (3.0)	0 (0.0)	5 (15.2)	3 (9.1)	0 (0.0)	0 (0.0)
	Thrombocytopenia	2 (6.1)	3 (9.1)	2 (6.1)	0 (0.0)	3 (9.1)	4 (12.1)	0 (0.0)	0 (0.0)
	Febrile neutropenia	1 (3.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Non haematological									
	Allergic reactions	1 (3.0)	2 (6.1)	0 (0.0)	0 (0.0)	2 (6.1)	1 (3.0)	1 (3.0)	0 (0.0)
	Fatigue	15 (45.5)	9 (27.3)	1 (3.0)	0 (0.0)	9 (27.3)	2 (6.1)	0 (0.0)	0 (0.0)
	Alopecia	12 (36.4)	8 (24.2)	3 (9.1)	0 (0.0)	8 (24.2)	10 (30.3)	3 (9.1)	0 (0.0)
	Sensory neuropathy	6 (18.2)	4 (12.1)	0 (0.0)	0 (0.0)	12 (36.4)	8 (24.2)	0 (0.0)	0 (0.0)
	Arthralgia	4 (12.1)	0 (0.0)	0 (0.0)	0 (0.0)	5 (15.2)	2 (6.1)	0 (0.0)	0 (0.0)
	Liver function damage	5 (15.2)	5 (15.2)	0 (0.0)	0 (0.0)	8 (24.2)	0 (0.0)	0 (0.0)	0 (0.0)
	Nausea	7 (21.2)	0 (0.0)	0 (0.0)	0 (0.0)	4 (12.1)	1 (3.0)	0 (0.0)	0 (0.0)
	Vomiting	3 (9.1)	0 (0.0)	0 (0.0)	0 (0.0)	2 (6.1)	1 (3.0)	0 (0.0)	0 (0.0)
	Constipation	5 (15.2)	1 (3.0)	0 (0.0)	0 (0.0)	5 (15.2)	1 (3.0)	0 (0.0)	0 (0.0)
	Diarrhoea	4 (12.4)	1 (3.0)	0 (0.0)	0 (0.0)	4 (12.4)	0	0 (0.0)	0 (0.0)

and gemcitabine/cisplatin as first-line treatments for MBC, that PFS of gemcitabine/paclitaxel was 4.8 months (95% CI, 4.2 to 7.0). Although the doses of gemcitabine (2,500 mg/m^2) and paclitaxel (150 mg/m^2) were higher than in our study. The PFS of TG in our study was longer compared with these two trials. The patients in our study who finished 6 cycles of TG switched to maintenance therapy with paclitaxel. Studies have shown a survival advantage with longer chemotherapy administration in MBC, thus supporting a policy of prolonging treatment until disease progression in the absence of unacceptable toxicity [16,17].

Maintenance chemotherapy in MBC has also prolonged PFS, but has had conflicting results in terms of OS [17-19]. Maintenance chemotherapy with paclitaxel/gemcitabine (PG) was superior to observation in PFS (7.5 vs 3.8 months, respectively; p=0.026). The median OS time was longer in the maintenance group than in the observation group (32.3 vs 23.5 months, respectively;p=0.047) [20]. However, the extension of full-dose chemotherapy after disease control may be considered an outdated concept and may not be feasible because of excessive toxicity and a negative impact on quality of life.

The optimal design of maintenance studies in MBC, including the choice of the chemotherapeutic agent, duration of treatment, and the most suitable patient population is not clear. Switching to single-agent maintenance therapy represents a new treatment approach for patients discontinuing combination chemotherapy before disease progression. For this reason, both the combination and the sequential regimen were switched to single agent paclitaxel maintenance therapy in our study to prolong the TTP. The MANTA1 trial [21], which compared maintenance paclitaxel with no further therapy in MBC patients not experiencing progression after first-line anthracycline/paclitaxel chemotherapy, showed that the median TTP for maintenance paclitaxel was 8 months (95% CI, 7 to 12 months) versus 9 months (95% CI, 7 to 13 months) for those who stopped chemotherapy (p=0.817). The results provide strong evidence against the hypothesis that maintenance paclitaxel is associated with a clinically worthwhile effect on PFS. The lack of benefit of maintenance paclitaxel may be attributable to the induction chemotherapy or the younger patients. A small Spanish multicentre study also evaluated paclitaxel maintenance after anthracycline and taxane therapy, but in this case the randomization occurred before the upfront therapy was administered, and the maintenance consisted of weekly paclitaxel (60 mg/m^2). Although longer in the maintenance arm, PFS was not significantly different (12 vs 8 months, p=0.1), and OS was 24 months in both arms [22].

The median PFS of patients who did not receive maintenance therapy in the combination arm (20 cases) and the sequential arm (21 cases) had

no significant difference (p=0.197;Figure 4). The results of our study in terms of PFS between combination and sequential arm were independent of maintenance therapy.

A limitation of previous trials comparing combination and sequential regimens was that traditional drugs, such as anthracyclines and taxanes, were used, not the modern drugs. The prognosis of advanced breast cancer has significantly improved over time, possibly due to the availability of newer active agents and to amelioration of supportive care [23-25]. Tomova et al. [8] compared the TTP of concomitant docetaxel plus gemcitabine with sequential docetaxel and gemcitabine. Although terminated prematurely, this prospective randomized trial demonstrated that no significant difference was observed in terms of TTP, ORR, residual disease,or OS.

Our trial is the first formal comparison of gemcitabine and paclitaxel combination chemotherapy with a sequential treatment design. The overall incidence of treatment-related adverse events was similar in both arms; also, no significant difference was found in the total number of serious adverse events. However, the incidence of neutropenia was significantly higher in the concomitant arm (90.9%) than in the sequential arm (60.6%), while grade 3 or 4 neutropenia was not significantly different between the two arms.

In conclusion, this trial found that sequential paclitaxel and gemcitabine clearly trended toward prolonged PFS and less bone marrow suppression. We would further expand the sample size to confirm the better benefit of the sequential arm. In future trials, new cytotoxic agents and novel formulations of existing drugs should be adapted for use in clinical practice for the management of MBC patients..

Conflict of interests

The authors declare no conflict of interests.

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