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Gemcitabine and split-dose paclitaxel or docetaxel in metastatic breast cancer: A randomised phase II study ☆

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ABSTRACT

Purpose: The purpose was to evaluate the activity and toxicity of split-dose paclitaxel or docetaxel in combination with gemcitabine in patients with metastatic breast cancer (MBC) who had previously received anthracyclines.

Patients and methods: A total of 210 patients were randomly assigned to one of three treatment arms: gemcitabine 1250 mg/m^2 Days 1 and 8 and paclitaxel 175 mg/m^2 as a 3-h infusion on Day 1 (GP1); gemcitabine 1000 mg/m^2 Days 1 and 8 and paclitaxel 100 mg/m^2 as a 1-h infusion on Days 1 and 8 (GP2); gemcitabine 1000 mg/m^2 Days 1 and 8 and docetaxel 40 mg/m^2 as a 1-h infusion on Days 1 and 8 (GD). Cycles were repeated every 3 weeks.

Results: For the 204 patients evaluable for response assessment, the response rates were 48.6% for GP1, 52.2% for GP2, and 52.3% for GD. Median response duration, time to treatment failure, and time to progression (TTP) were similar in each arm. Median TTP for GP1, GP2 and GD was 7.5, 7.0 and 7.4 months, respectively. For the 208 patients evaluable for safety, the most common grade 3/4 toxicity for each regimen was neutropaenia, with 64%, 57%, and 68% for GP1, GP2, and GD, respectively. Grade 4 neutropaenia, grade 3/4 anaemia, febrile neutropaenia, and diarrhoea were more common in the docetaxel arm, as was the use of intravenous antibiotics and blood transfusions.

Conclusion: The study confirmed the high activity of gemcitabine–taxane combinations in MBC. Split-dose paclitaxel had similar activity and toxicity to the 3-weekly administration. The split-dose docetaxel regimen had similar activity to the paclitaxel combinations though associated with higher toxicity.

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1. Introduction

Cytotoxic chemotherapy is the mainstay of treatment for patients with hormone-insensitive metastatic breast cancer (MBC). Anthracyclines and taxanes are considered the most active agents. Recent research has focused on sequential single agent versus concurrent combination chemotherapy and taxane scheduling. Originally, paclitaxel and docetaxel were generally administered once every 3 weeks. More recently, Phase II studies have shown encouraging activity and safety for weekly taxane administration.[1–6] Weekly taxane administration alters the toxicity profile compared to the 3-weekly schedule. It lowers the incidence of severe neutropaenia and acute non-haematological toxicity while cumulative clinical adverse events such as fatigue, asthenia, and neuropathy are more common and severe.

The anti-metabolite gemcitabine has shown encouraging Phase II activity in MBC. When used as a single agent, response rates ranged from 14% to 37%, dependent mostly on the extent of prior chemotherapy.[7–10] Gemcitabine and taxanes have differing toxicity profiles and have shown synergy in preclinical models.[11,12] Thus, gemcitabine appears to be an attractive candidate for combination with taxanes. Phase II studies of gemcitabine with either paclitaxel or docetaxel have shown response rates of 36–79% in MBC, with median time to progression from 7 to 16 months and median survival of around 12 months.[13–18] Toxicity was generally well manageable, with neutropaenia being dose-limiting.

The current randomised Phase II study was an extension to the themes of taxane scheduling and gemcitabine-taxane combinations in MBC. The primary aim was to explore whether combinations of gemcitabine with paclitaxel or docetaxel given on Days 1 and 8 of 3-weekly treatment cycles (termed split-dose) are promising for future Phase III evaluation. At the time this study was designed a prospective randomised Phase III study of paclitaxel with versus without gemcitabine was underway that used a 3-weekly paclitaxel schedule. The same gemcitabine–paclitaxel regimen was used in one arm of the present study to serve as an internal reference for the split-dose arms and to evaluate whether the global data are reproducible in a mostly Asian population.

2. Patients and methods

2.1. Patient eligibility

Eligible patients for this study (B9E-MC-S197) had histologic or cytologic diagnosis of breast carcinoma and stage IV disease. Patients must have received prior chemotherapy with doxorubicin or epirubicin, which could be for adjuvant therapy or treatment for locally advanced or metastatic disease. Prior adjuvant chemotherapy with paclitaxel or docetaxel was allowed if the interval between the last dose of taxane and disease recurrence was at least 12 months. In addition to the anthracycline treatment, patients may have received one other prior chemotherapy regimen in the adjuvant, locally advanced, or metastatic setting. Other inclusion criteria included: Karnofsky performance status (KPS) of 70 or higher and estimated life expectancy of at least 12 weeks; age of at least 18 years; white blood cell (WBC) count $\geqslant 3.5 \times 10^9$/L; absolute neutrophil count (ANC) $\geqslant 1.5 \times 10^9$/L; platelets $\geqslant 100 \times 10^9$/L; haemoglobin $\geqslant 90$ g/L; total serum bilirubin $\leqslant 1.5 \times$ upper limit of normal (ULN); alanine aminotransferase (ALT) or aspartate aminotransferase (AST) $\leqslant 2.5 \times$ ULN for patients without liver metastasis, $\leqslant 5 \times$ ULN for patients with liver metastasis; bi-dimensionally measurable disease. Exclusion criteria included: prior treatment with a taxane for locally advanced or metastatic disease; prior treatment with gemcitabine; any other concomitant anti-tumour therapy; pregnancy or breast feeding; unstable diabetes mellitus; other documented malignancy; peripheral neuropathy of $\geqslant$Common Toxicity Criteria (CTC) grade 2. The study was conducted according to according to The International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceutical for Human Use (ICH) good clinical practice guidelines, including obtaining written informed consent from all patients and with the approval of the local research ethics committee at each participating institution.

2.2. Study design and treatments

Patients were randomised with equal probability to one of three arms using an automated voice recognition system stratified by investigating centre with a block size of six. Randomisation was done centrally. In each arm gemcitabine was administered by intravenous infusion over 30 min on Days 1 and 8 of a 21-day cycle. In the GP1 arm, gemcitabine was given at a dose of 1250 mg/m^2, combined with paclitaxel 175 mg/m^2 given by intravenous infusion over 3 h on Day 1 of each 21-day cycle. In the GP2 arm, gemcitabine was given at a dose of 1000 mg/m^2, combined with paclitaxel 100 mg/m^2 given by intravenous infusion over 1 h on Days 1 and 8 of each 21-day cycle. In the GD arm, gemcitabine was given at a dose of 1000 mg/m^2, combined with docetaxel 40 mg/m^2 given by intravenous infusion over 1 h on Days 1 and 8 of each 21-day cycle. A maximum of eight cycles was allowed. Patients receiving paclitaxel had standard pre-medication with intravenous dexamethasone, diphenhydramine (or another antihistamine of equivalent strength), and cimetidine. Patients receiving docetaxel had standard 3-day co-medication with oral dexamethasone around the day of docetaxel administration. Prophylactic use of haemopoietic growth factors was not allowed in this study. Therapeutic use of granulocyte colony stimulating factor (G-CSF) was allowed in case of ANC $< 0.5 \times 10^9$/L, neutropaenic fever, or documented infections while neutropaenic.

2.3. Dose adjustments for haematologic toxicity

To start the next cycle, ANC had to be $\geqslant 1.5 \times 10^9$/L and platelets $\geqslant 100 \times 10^9$/L. Dose adjustments were based on the nadir counts from the preceding cycle. The doses of gemcitabine, paclitaxel, and docetaxel (as appropriate) were reduced by 20% in the subsequent cycle (and remainder of the study) in the case of the following: (i) ANC 0.5–0.99×10^9/L associated with documented infection or fever and platelets $\geqslant 25 \times 10^9$/L; (ii) ANC $< 0.5 \times 10^9$/L lasting for $\geqslant 7$ days or associated with documented infection or fever and platelets $\geqslant 25 \times 10^9$/L; (iii) platelets 25–49.9×10^9/L if associated with bleeding; or (iv) platelets $<25 \times 10^9$/L. If a patient with a prior dose reduction

would require a second dose reduction then they were discontinued from the study. Treatment could be delayed for up to 42 days from Day 1 of the current cycle. Dose adjustments on Day 8 were based on haematology values for Day 8 of the present cycle and had no effect on dosing in the following cycle.

2.4. Dose adjustments for non-haematologic toxicity

If serum bilirubin was increased to >1.5 × ULN or AST/ALT increased to >2.5 × ULN in patients without liver metastasis and >5.0 in patients with liver metastasis at the start of the next cycle then the cycle could not begin until serum bilirubin returned to ⩽1.5 × ULN and AST/ALT returned to ⩽2.5 × ULN in patients without liver metastasis and ⩽5.0 × ULN in patients with liver metastasis. If the values did not return to these limits within 42 days from Day 1 of the current cycle then the patient was discontinued from the study. The doses of gemcitabine, paclitaxel, and docetaxel (as appropriate) were reduced by 20% in the subsequent cycle(s) if serum bilirubin was increased 2-fold or AST/ALT was increased 5-fold relative to baseline at any time during the cycle. Dose adjustments on Day 8 for hepatic toxicity had no effect on dosing in subsequent cycles. In the case of grade 2 peripheral neuropathy, the dose of paclitaxel or docetaxel was reduced by 20% in all subsequent cycles. Treatment was discontinued if these toxicities were of grade 3 or 4. In the case of grade 2 myalgia, arthralgia, asthenia, or fatigue, the gemcitabine and paclitaxel or docetaxel doses were reduced by 20% in all subsequent cycles. Treatment was discontinued if these toxicities were of grade 3 or 4. In the event of grade 3 skin toxicity, continuation of study treatment was at the discretion of the investigator; if treatment was continued, the doses of gemcitabine and paclitaxel were reduced by 20%. Treatment was discontinued in the case of grade 4 skin toxicity.

2.5. Study parameters

Before enrolment in the study patients were required to have a physical examination, computed tomography (CT) scan of the abdomen, chest X-ray with or without CT scan of the thorax, and complete blood work-up. Before the start of each cycle and the Day 8 dosing, a physical examination, full blood count, and blood work-up were performed. A full blood count was obtained around Day 15.

Tumour response status was evaluated every two cycles (approximately 6 weeks). Confirmation of response was required 3–4 weeks from the date of first documentation of response. The World Health Organization (WHO) criteria for evaluation of response were used, with slight modifications as described. Complete response was defined as complete disappearance of all known disease; partial response as at least 50% reduction in the size of measurable lesions; stable disease as less than 50% reduction and 25% increase in the size of measurable lesions; and progressive disease as equal to or more than 25% increase in the size of at least one measurable lesion or any appearance of a new lesion. If a patient had a complete or partial response at the time of discontinuation of study the therapy response status was evaluated every 2 months until documented disease progression, death, or 12 months after study enrolment, whichever occurred first. Toxicity was graded according to the National Cancer Institute Common Toxicity Criteria, version 2.0.[19]

2.6. Statistical methods

The primary objective of this study was to evaluate the response rate of the three gemcitabine–taxane combinations. A planned sample size of 70 patients for each arm was chosen to provide 89% power to rule out a response rate of 40% or lower given a true response rate of 60%. Secondary objectives were toxicity, duration of response (defined as the time from randomisation to disease progression in patients for whom the response had been confirmed), time to treatment failure (defined as time from randomisation to early discontinuation of therapy for any reason or disease progression if all planned therapy was completed, but censored if the patient was lost to follow-up or moved), and time to disease progression (defined as time from randomisation to disease progression or death due to study disease). Time to event variables were censored at the date of last contact. For time to event variables, hazard ratios were estimated with Cox proportion hazards modelling, and log-rank *p*-values are reported. Fisher's Exact *p*-values for differences in proportions are provided unless otherwise stated. Statistical analyses were conducted using SAS v.8.2. The current study was designed to determine estimates of efficacy and toxicity in each treatment arm separately, not to formally compare outcomes between groups. However, *post hoc* comparative statistics were performed on the relative efficacy and toxicity of the treatments. As these analyses and data are purely exploratory no *p*-values are reported. This study was exploratory in nature and there were no pre-defined thresholds for the decision to go to a Phase III trial.

3. Results

3.1. Patient characteristics and disposition

Between July 2001 and January 2003, 210 patients were enrolled in this study (Fig. 1). Two hundred and eight patients were evaluable for safety and time-to-event efficacy analysis and 204 patients for response assessment. Of the 6 patients who did not qualify for response assessment, 3 patients did not meet the eligibility criteria (Arm GD), 2 patients received no study therapy (1 Arm GP1, 1 Arm GP2), and 1 patient died of cardiac failure unrelated to study therapy before receiving a full cycle of therapy (Arm GP2). Of the 204 patients, 198 (97%) were Asian. The three treatment groups had similar baseline characteristics (Table 1). Dominant site of metastasis was visceral in 70% of patients, with liver involvement in 35%. More than 50% of patients had three or more organ sites involved by disease. All but 1 patient had previously received treatment with anthracyclines, 46% for MBC. Of the 109 patients who had received prior chemotherapy for MBC, the best response to any line of prior therapy was complete response (CR) in 5 patients (4.6%), partial response (PR) in 17 (15.6%), and progressive disease (PD) in 65 (59.6%).

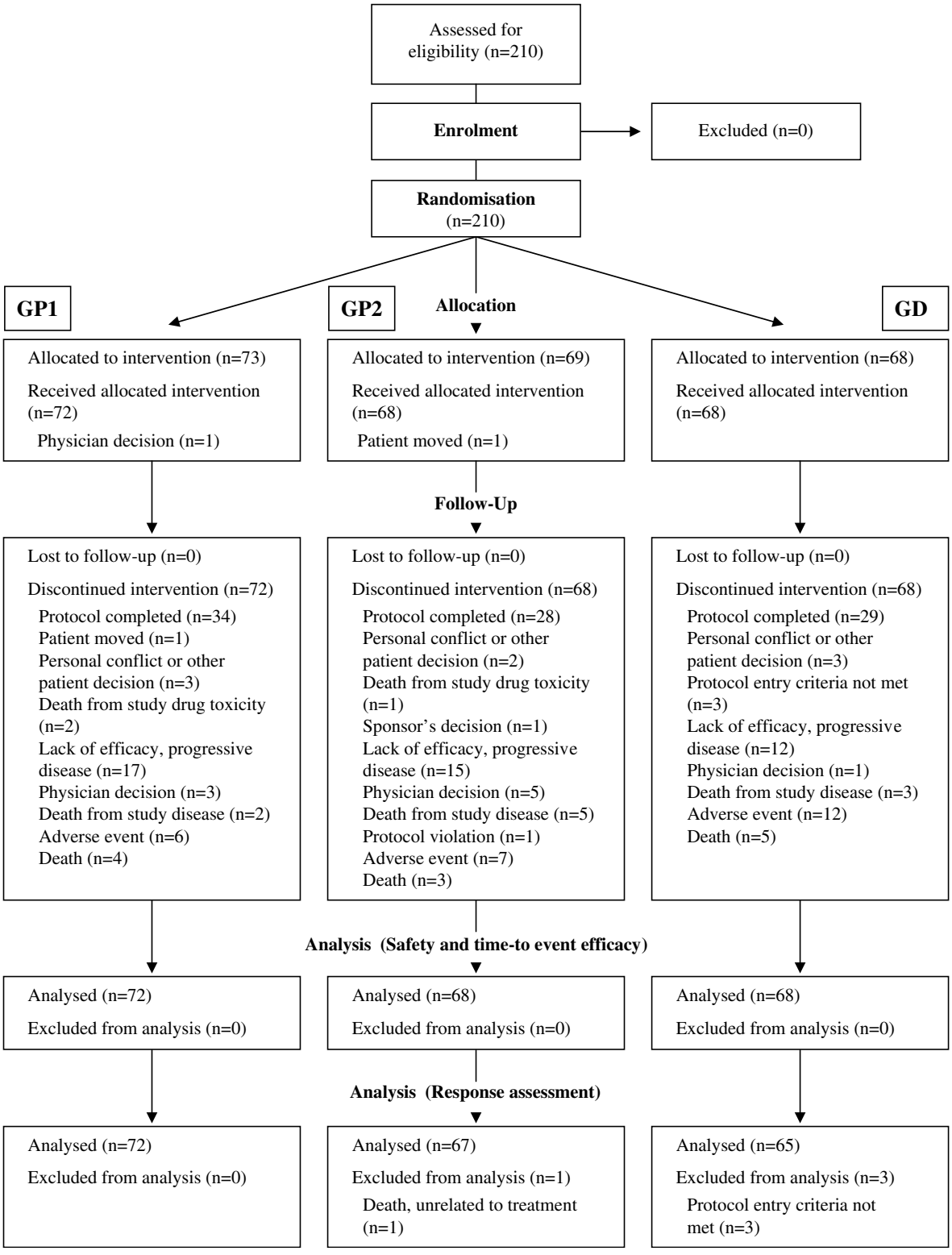

Fig. 1 – Study flowchart.

3.2. *Efficacy*

The three arms showed similar efficacy outcomes, with a response rate of 48.6% for the GP1 arm, 50.3% for the GP2 arm, and 52.3% for the GD arm (Table 2). In total, there were 10 CRs (4.9%) and 94 PRs (46.1%), for an overall response rate for the 204 patients evaluable for response assessment of 51.0% (95% confidence interval (CI): 43.9% to 58.0%). Median response duration, time to treatment failure, and time to progression were similar in each arm (Table 2). The Kaplan–Meier curves

Table 1 – Patient and tumour characteristics

	GP1 ($n = 72$)	GP2 ($n = 67$)	GD ($n = 65$)
Age, median (years)	48	47	48
Age, range (years)	29–72	23–71	20–77
KPS, median	90	90	90
KPS, range	70–100	70–100	70–100
Dominant site of disease			
Visceral	51 (70.8%)	48 (71.6%)	44 (67.7%)
Bone	6 (8.3%)	6 (9.0%)	5 (7.7%)
Soft tissue	15 (20.8%)	13 (19.4%)	16 (24.6%)
Number of organ sites			
1	17 (23.6%)	13 (19.4%)	9 (13.6%)
2	20 (27.8%)	18 (26.9%)	22 (33.8%)
$\geqslant 3$	35 (48.6%)	36 (53.7%)	34 (52.3%)
Number of lines of prior chemotherapy for MBC			
0	38 (52.8%)	26 (38.8%)	31 (47.7%)
1	28 (38.9%)	33 (49.3%)	31 (47.7%)
2	6 (8.3%)	8 (11.9%)	2 (3.1%)
3	0	0	1 (1.5%)
Prior anthracycline therapy			
As adjuvant therapy	44 (61.1%)	29 (43.3%)	37 (56.9%)
For advanced disease	28 (38.9%)	37 (55.2%)	29 (44.6%)
Prior taxane as adjuvant therapy	0	0	1 (1.5%)
Other prior chemotherapy			
Adjuvant chemotherapy	11 (15.3%)	16 (23.8%)	9 (13.8%)
For advanced disease	12 (16.7%)	11 (16.4%)	7 (10.8%)
Prior hormonal therapy	25 (34.7%)	30 (44.8%)	28 (43.1%)

Abbreviations: KPS, Karnofsky performance status; MBC, metastatic breast cancer.

for time to disease progression and time to treatment failure are shown in Figs. 2 and 3.

3.3. *Toxicity*

CTC grade 3 or 4 haematological toxicity was observed in 70.2% of the 208 patients evaluable for safety (GP1, 66.7%; GP2, 64.7%; GD, 79.4%), and CTC grade 3 or 4 non-haematological toxicity was seen in 49.0% of these patients (GP1, 52.8%; GP2, 39.7%; GD, 54.4%). Individual grade 3 and 4 haematological and non-haematological toxicities are shown in Table 3. The most common grade 3 or 4 haematological toxicity in each arm was neutropaenia, experienced by 63.0% of all patients (GP1, 63.9%; GP2, 57.3%; GD, 67.7%). Grade 4 neutropaenia, grade 3/4 anaemia, febrile neutropaenia, and grade 3/4 diarrhoea were more common in the GD arm than in the gemcitabine–paclitaxel arms, as was the use of supportive therapy such as therapeutic use of G-CSF, intravenous antibiotics, and blood transfusions (Table 4). The death of 6 patients was considered probably or possibly related to study therapy (2 on GP1, 3 on GP2, 1 on GD). These deaths were mostly due to myelotoxicity: 3 patients died of infection secondary to neutropaenia, 1 patient of intracranial haemorrhage secondary to pancytopaenia, and 2 patients died of acute renal failure.

Table 2 – Efficacy outcomes

	GP1	GP2	GD	Overall
Response rate	$n = 72$	$n = 67$	$n = 65$	$n = 204$
Complete response	3 (4.2%)	4 (6.0%)	3 (4.6%)	10 (4.9%)
Partial response	32 (44.4%)	31 (46.3%)	31 (47.7%)	94 (46.1%)
Stable disease	13 (18.1%)	13 (19.4%)	15 (23.1%)	41 (20.1%)
Progressive disease	15 (20.8%)	13 (19.4%)	7 (10.8%)	35 (17.2%)
Not done	7 (9.7%)	3 (4.5%)	5 (7.7%)	15 (7.4%)
Unknown	2 (2.8%)	3 (4.5%)	4 (6.2%)	9 (4.4%)
Time-to-event measures	$n = 35$	$n = 35$	$n = 34$	$n = 104$
Median response duration (months)	8.3	8.2	7.8	8.2
	$n = 72$	$n = 68$	$n = 68$	$n = 208$
Time to treatment failure (months)	6.3	5.5	6.5	6.1
Time to progression (months)	7.5	7.0	7.4	7.1

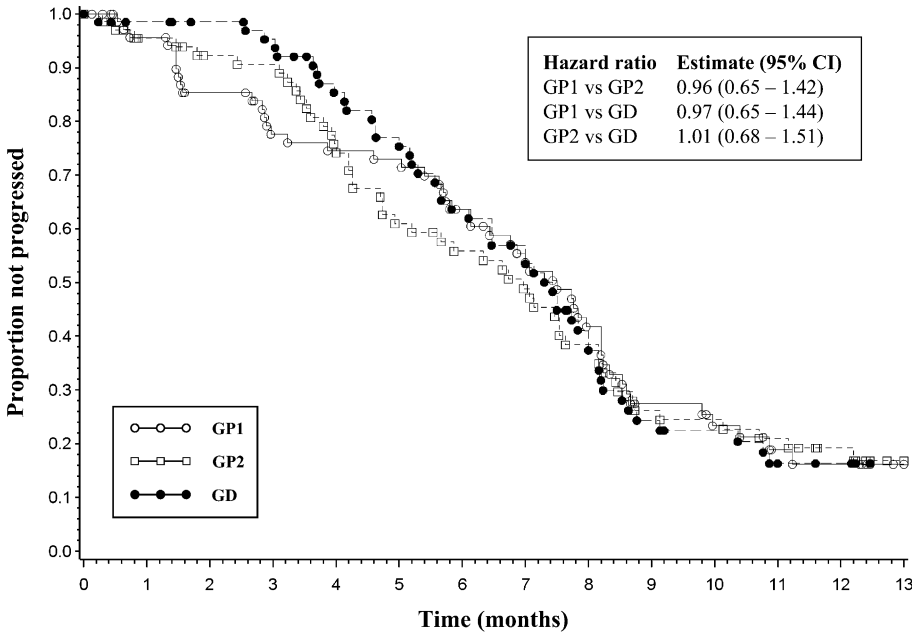

Fig. 2 – Time to disease progression by treatment arm.

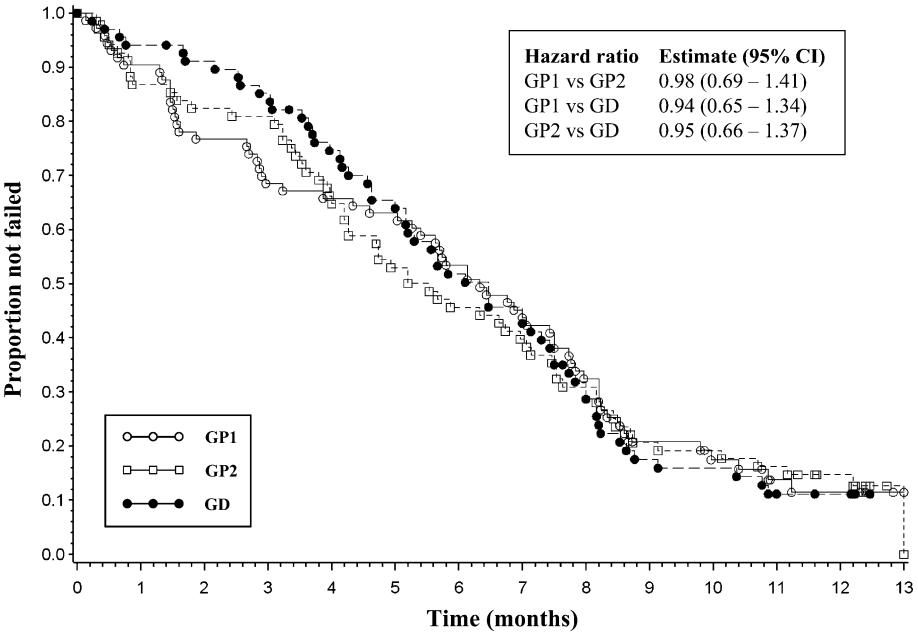

Fig. 3 – Time to treatment failure by treatment arm.

The median number of cycles per patient was 7, 6, and 7 for the GP1, GP2, and GD arms, respectively. The mean dose intensity of gemcitabine achieved in GP1, GP2, and GD was 661.6, 522.5, and 547.4 mg/m^2/week, respectively. The planned dose intensity of paclitaxel was 58.3 mg/m^2/week in the GP1 arm and 66.7 mg/m^2/week in the GP2 arm. The mean dose intensity of paclitaxel achieved in GP1 and GP2 was similar (53.3 and 52.2 mg/m^2/week, respectively). The mean relative dose intensity of paclitaxel was significantly higher in GP1 than GP2 (91.4% versus 78.9%, $p < 0.0001$). The mean relative dose intensity of docetaxel in GD was 82.1%. The proportion of cycles with dose adjustment of paclitaxel was 15.0% in GP1 and 49.2% in GP2. Dose adjustment of docetaxel in GD was required in 45.9% of cycles. Most patients on GP2 (89.7%) and GD (83.8%) required at least one delay or reduction in paclitaxel and docetaxel dose, respectively, while this was the case in only 51.4% of patients on GP1. The proportion of cycles with delay or reduction in the gemcitabine dose was around 50% in each arm.

3.4. *Exploratory adjustment for baseline covariates*

The pre-specified analyses were within-group estimates of response rates, and as such were not adjusted for imbalance

Table 3 – Grade 3 and 4 toxicities (%)

	GP1 (n = 72) (%)		GP2 (n = 68) (%)		GD (n = 68) (%)	
Grade	3	4	3	4	3	4
Leukopaenia	33.3	9.7	41.2	8.8	39.7	19.1
Neutropaenia	45.8	18.1	39.7	17.6	36.8	30.9
Thrombocytopaenia	16.7	1.4	14.7	0	22.1	0
Anaemia	8.3	0	8.8	1.5	19.1	4.4
Febrile neutropaenia	0	0	2.9	1.5	7.4	4.4
Infection	1.4	5.6	4.4	1.5	8.8	4.4
Bleeding	2.8	1.4	0	1.5	1.5	1.5
ALT	15.3	0	10.3	0	7.4	0
AST	13.9	0	4.4	0	7.4	0
GGT	0	0	0	0	1.5	0
Bilirubin	4.2	0	2.9	1.5	0	1.5
Diarrhoea	2.8	0	2.9	0	7.4	5.9
Dyspnea	8.3	1.4	2.9	1.5	4.4	5.9
Fatigue/asthenia	2.8	2.8	10.3	0	5.9	1.5
Nausea	1.4	0	0	0	0	0
Vomiting	2.8	0	2.9	0	1.5	0
Skin toxicity	2.8	0	0	0	2.9	0
Arthralgia/myalgia	4.2	0	1.5	0	0	0
Polyneuropathy	2.8	0	1.5	0	1.5	0
Hypersensitivity reaction	0	1.4	1.5	1.5	0	0
Oedema	1.4	0	0	0	1.5	0

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; GGT, gamma-glutamyl transpeptidase.

Table 4 – Supportive therapy

Supportive therapy	GP1 (n = 72) (%)	GP2 (n = 68) (%)	GD (n = 68) (%)	p-value
Therapeutic G-CSF	9.7	10.3	17.6	0.339
IV antibiotics	15.3	14.7	35.3	0.0062
Whole blood	1.4	7.4	10.3	0.0625
Packed red cells	4.2	1.5	17.6	0.0009

Abbreviations: G-CSF, granulocyte colony stimulating factor.

between the treatment groups in baseline prognostic indicators. To investigate whether baseline imbalances could have significantly altered the conclusions, the odds ratio for response rates and hazard ratios for the time to event analyses were compared before and after adjusting for potential confounding factors such as extent of prior chemotherapy, dominant site of disease (soft tissue, visceral or bone), three or more organ sites involved, and prior hormonal therapy. The estimates for the adjusted and unadjusted exploratory comparisons are shown in Table 5. Overall, there was no evidence to suggest that the pre-defined unadjusted analyses had failed to identify a large treatment effect that was being obscured by confounding baseline factors. However, there is an indication the unadjusted overall response rate in the GP2 arm may have been under-estimated relative to the other arms, due to the greater amount of prior therapy in this arm.

Table 5 – Exploratory adjustment for baseline covariates

	GP1 versus GP2	GP2 versus GD	GP1 versus GD
Response rate (odds ratio)			
Unadjusted	0.86 (0.44–1.68)	1 (0.5–1.97)	0.86 (0.44–1.69)
Adjusted[a]	0.69 (0.34–1.41)	1.22 (0.59–2.52)	0.84 (0.41–1.72)
TTPD (hazard ratio)			
Unadjusted	0.96 (0.65–1.42)	1.01 (0.68–1.5)	0.97 (0.65–1.44)
Adjusted[a]	0.96 (0.64–1.44)	0.99 (0.66–1.48)	0.95 (0.63–1.42)
Duration of tumour response (hazard ratio)			
Unadjusted	0.73 (0.42–1.28)	0.85 (0.5–1.43)	0.62 (0.36–1.08)
Adjusted[a]	0.68 (0.38–1.21)	0.84 (0.49–1.44)	0.57 (0.33–1)

Abbreviations: TTPD, time to progressive disease.
a Adjusted for extent of prior chemotherapy, dominant site of disease (soft tissue, visceral, or bone), three or more organ sites involved, and prior hormonal therapy.

4. Discussion

Combinations of gemcitabine and paclitaxel or docetaxel have shown early promise in MBC.[13–18] This was confirmed in the present study with an overall response rate of 51.0% in a total of 204 evaluable patients. Response rate and duration, time to treatment failure, and time to progression seemed encouraging for a patient population that had prior treatment with anthracyclines, visceral metastasis as dominant site in 70%, and at least three or more organ sites of disease in more than 50%.

A recently reported global Phase III study of gemcitabine–paclitaxel versus single-agent paclitaxel in patients with MBC who had prior anthracycline therapy has shown significantly superior response rate (39.3% versus 25.6%, $p = 0.0007$) and time to progression (5.4 versus 3.5 months, $p = 0.0013$) in favour of the combination.[20] An interim overall survival analysis also clearly favoured the combination arm,[21] with a median survival of 18.5 versus 15.8 months (hazard ratio 0.775, 0.63–0.96) and a 1-year survival rate of 70.7% versus 60.9% ($p = 0.019$). Patients on gemcitabine–paclitaxel experienced better quality of life and pain control.[20] Importantly, the combination was very well tolerated. It was associated with higher haematologic toxicity than single-agent paclitaxel but there was little difference in clinical adverse events.[20] The GP1 arm in the present study used the same doses and schedule of gemcitabine and paclitaxel. The efficacy and toxicity of GP1 in this largely Asian population was comparable to the experience in the global trial. The somewhat better efficacy outcomes in the present study are well within the range of what is typically seen in comparisons of data across studies, particularly Phase II and III trials.

Optimisation of paclitaxel scheduling continues to be a major focus of research in breast cancer. Data from uncontrolled Phase II studies showed encouraging activity for weekly paclitaxel, coupled with good patient tolerance. The recently reported CALGB 9840 trial has provided Phase III evidence of superior efficacy of weekly versus 3-weekly paclitaxel in MBC.[22] GP2 in the present study used paclitaxel at 100 mg/m^2 on Days 1 and 8 every 3 weeks, a schedule we termed split-dose. In contrast to weekly paclitaxel, GP2 offered a 2-week treatment break for patients while maintaining a higher dose density than the 3-weekly GP1. In addition to more convenience for patients and caregivers, we hypothesised that the treatment break in GP2 may reduce the risk of cumulative clinical toxicity associated with weekly taxanes while maintaining the benefit of lower acute toxicities compared to the 3-weekly schedule and high efficacy. The numerical efficacy was similar for all three regimens, however, given the width of the confidence intervals and that the study was not designed to formally compare the treatments, it is not possible to conclude equivalence. The rate of cumulative clinical toxicity was low and not different for GP2 versus GP1. However, despite a lower planned and achieved dose intensity of gemcitabine the acute haematological and non-haematological toxicities of GP2 were not less common or severe, and close to 90% of patients on GP2 required dose reductions or omissions of paclitaxel while less than 50% on GP1 did so. Taken together, this study did not suggest that split-dose paclitaxel offers an advantage over 3-weekly paclitaxel in MBC when used in combination with gemcitabine. However, due to random chance patients in the GP2 arm did have more extensive prior chemotherapy than patients in the other two arms. Retrospective adjustment of the response rates for this difference suggests that the observed response rate may have underestimated the true efficacy of the GP2 arm. Such retrospective adjustments should not be taken as conclusive, but this points to a potential efficacy benefit of split-dose paclitaxel in combination with gemcitabine that seems to warrant further investigation.

Of interest, a recent Phase II trial reported high activity and good tolerance of gemcitabine and paclitaxel given every 2 weeks at a dose of 2500 and 150 mg/m^2, respectively.[23] In this uncontrolled single-arm study the response rate in 42 evaluable patients was 71%, including 26% complete remissions. The median time to progression was more than 16 months. It should be noted that key patient characteristics differed compared to the present trial and the global randomised Phase III study. Patients were not allowed to have prior chemotherapy for MBC, 49% of patients had no prior chemotherapy altogether, only 32% had prior adjuvant anthracyclines, and more than 50% of patients did not have visceral disease.

The efficacy shown by gemcitabine and split-dose docetaxel appears in line with previously reported Phase II data of gemcitabine and 3-weekly, weekly, or bi-weekly docetaxel.[14–16,18,24,25] Indirect evidence has suggested docetaxel to have higher efficacy than paclitaxel in MBC.[26,27] Recently, a randomised Phase III trial prospectively compared docetaxel and paclitaxel in patients with MBC who had previously received anthracyclines.[28] The study found significantly longer median time to progression and overall survival for the docetaxel arm. The response rate was also higher with docetaxel but this was not statistically significant. The present study did not suggest split-dose docetaxel in combination with gemcitabine to have higher efficacy than the gemcitabine–paclitaxel combinations, although the size of the confidence intervals means that an important difference in either direction cannot be ruled out. A recent Phase III trial showed superior response rate, time to progression, and survival for a combination of docetaxel and capecitabine versus single-agent docetaxel in patients with MBC who had prior anthracycline therapy.[29] Haematological and non-haematological toxicity of the combination were substantial. In the current study, severe toxicity was more common on GD than on either gemcitabine–paclitaxel combination, specifically haematologic toxicity, febrile neutropaenia, and diarrhoea. This was associated with a higher need for supportive care measures such as therapeutic G-CSF, intravenous antibiotics, and blood transfusions. Similar to GP2, cumulative non-haematological toxicity was rare with split-dose docetaxel and gemcitabine. Taken together, the present study showed higher toxicity for gemcitabine and split-dose docetaxel as compared to the combinations with paclitaxel.

The higher toxicity observed with GD is in accordance with the findings from the Phase III study of docetaxel and paclitaxel where docetaxel treatment was associated with a significantly higher incidence of neutropaenia, febrile neutropaenia, infection, stomatitis, diarrhoea, oedema, vomiting, asthenia, and neuromotor toxicity.[28] It should be noted that previous studies have suggested higher toxicity of docetaxel

in Asians versus Caucasians.[30–32] Docetaxel is hydroxylated by CYP3A4 and CYP3A5 to less active metabolites[33] and lower CYP3A activity has been found in Asians than Caucasians.[34] Accordingly, the toxicity of split-dose docetaxel and gemcitabine observed in the present study may be partly due to the largely Asian ethnicity of the patients.

In conclusion, the three gemcitabine–taxane combinations evaluated in this study showed encouraging efficacy in patients with MBC who had previously received anthracyclines. Split-dose paclitaxel showed similar efficacy and toxicity to the conventional 3-weekly administration. The split-dose docetaxel regimen had similar efficacy to the paclitaxel regimens, though potentially associated with more toxicity.

Conflict of interest statement

M.L. is an employee of Eli Lilly and Company and holds stocks in the company; W.H.H.R. is an employee of Eli Lilly and Company; K.S.K. has received honoraria from Eli Lilly and Company.

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