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Gemcitabine plus docetaxel versus capecitabine plus docetaxel for patients with anthracycline-pretreated metastatic breast cancer: a review of the results of a European Phase III trial

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Abstract

Gemcitabine plus paclitaxel has been shown to be efficacious and safe for the treatment of anthracycline-pretreated metastatic breast cancer (MBC) patients and was recently approved in this setting. The gemcitabine plus docetaxel combination has also been compared with capecitabine plus docetaxel as first- or second-line treatment for anthracycline-pretreated MBC patients. The trial compared progression-free survival, overall response rate, time to treatment failure, overall survival, toxicity and quality of life. The first results of this trial were reported recently at the American Society of Clinical Oncology (ASCO) meeting. Efficacy was similar in both groups. However, statistically significant differences were found in terms of toxicity. Non-haematological toxicity was low in both treatment arms. However, diarrhoea, mucositis and hand-and-foot syndrome were more pronounced in the capecitabine plus docetaxel arm. In addition, more frequent serious adverse events occurred in the capecitabine plus docetaxel arm, causing discontinuation in 28% of patients. There were two toxic deaths, both in the capecitabine plus docetaxel arm.

Keywords: Metastatic breast cancer; Gemcitabine plus docetaxel; Capecitabine plus docetaxel

1. Introduction

Breast cancer is the most common cancer in women [1]. A meta-analysis has shown that 6 months of anthracycline-based polychemotherapy reduces the annual breast cancer death rate by approximately 38% for women aged <50 years at diagnosis, and by approximately 20% for those aged 50–69 years at diagnosis, irrespective of treatment with tamoxifen and oestrogen receptor status [2]. Unfortunately, breast cancer recurs in 30–40% of patients and requires chemotherapy to palliate symptoms and improve quality of life (QoL).

For patients with recurrent breast cancer who have received prior treatment with anthracyclines, taxane-based chemotherapy is the standard therapy. A Phase III trial of single-agent docetaxel reported significantly superior overall survival (OS; 11.4 months vs 8.7 months; $P = 0.0097$) compared with a combination of mitomycin plus vinblastine in patients pretreated with anthracyclines, and has established single-agent docetaxel, at a dose of 100 mg/m^2, as one of the potential standards of care [3]. In addition, docetaxel has been widely studied as a single agent and has been shown to be highly active in the treatment of metastatic breast cancer (MBC) [4].

A subsequent Phase III study showed that the addition of oral capecitabine (1.25 mg/m^2 twice daily for 14 days) to docetaxel (75 mg/m^2) in a 21-day cycle resulted in a

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23% reduction in risk of death and an increase in median survival of 3 months compared with single-agent docetaxel (100 mg/m^2) [5]. QoL was similar in the two arms; however, when the combination was employed in everyday clinical practice, the experience was very different: diarrhoea, stomatitis and hand-and-foot syndrome prevented the completion of treatment in the majority of patients.

Docetaxel has been studied in combination with gemcitabine in several Phase II studies with overall response rates (ORR) in the range of 30% to 79% in patients who have received multiple lines of prior therapy, including paclitaxel regimens [6–11]. Mavroudis *et al.* included patients pretreated with paclitaxel. A higher than expected ORR of 54% was found in the patient population, which may suggest synergy between the two drugs [10]. Furthermore, the superiority of docetaxel in combination with capecitabine versus single-agent docetaxel in terms of efficacy has to be balanced against a significantly higher toxicity in this palliative setting [5]. The recent report by Albain *et al.* suggested that gemcitabine can be added to paclitaxel to improve efficacy in the treatment of MBC, with a high degree of tolerability [12]. Based on these results, a comparison of the efficacy and safety profile of gemcitabine plus docetaxel with that of capecitabine plus docetaxel is justified. We conducted such a trial, and communicated the results at ASCO 2005 [13].

2. Methods

This multicentre, Phase III randomised trial compared the efficacy and toxicity of gemcitabine plus docetaxel with capecitabine plus docetaxel in patients with MBC. The primary objective of the trial was to evaluate progression-free survival (PFS); secondary objectives included toxicity profile, QoL, OS, ORR, and time to treatment failure (TTF). Results of QoL and OS analyses are expected to be available by the end of 2005.

Eligible patients had a Karnofsky performance score of at least 70, were over 18 years of age, had a histologically or cytologically confirmed diagnosis of locally advanced or MBC and had received previous anthracycline-containing treatment. Patients were selected despite previous neoadjuvant or adjuvant treatment with taxanes, as long as it has been at least 6 months since completion of the regimen. Selection criteria stipulated that patients had measurable disease; measurable clinically (>2 cm in at least one dimension) or observed on a spiral computed tomography scan ($\geq$1 cm in at least one dimension). Patients were required to have an adequate bone marrow reserve (platelet count $\geq 100 \times 10^9$/L, neutrophil count $>1.5 \times 10^9$/L and haemoglobin $\geq$9.0 g/L), adequate liver function (amino alanine transferase [ALT] and aspartate amino transferase [AST] $<2.5 \times$ upper limit of normal range [ULN], normal bilirubin, alkaline phosphatase [AP] $\leq 2.5 \times$ ULN) and adequate renal function (creatinine $\leq 1.25 \times$ ULN, calcium $\leq 1.2 \times$ ULN). In the case of liver metastasis, acceptable liver function was defined as ALT and AST $\leq 3.5 \times$ ULN, AP $\leq 5 \times$ ULN and bilirubin $\leq 1.25 \times$ ULN.

A total of 305 patients were enrolled and randomised to receive gemcitabine plus docetaxel (153 patients) or capecitabine plus docetaxel (152 patients). Patients were randomised to each treatment arm according to the following prognostic factors: first- or second-line treatment for MBC, presence or absence of visceral disease, Karnofsky Performance status 70–80% or >80% and prior taxane treatment. Patients were randomised to receive: docetaxel (75 mg/m^2) on day 1 with gemcitabine (1 g/m^2) on days 1 and 8, every 21 days; or, docetaxel (75 mg/m^2) on day 1 and oral capecitabine (1,250 mg/m^2) twice daily on days 1–14 every 21 days. All patients were treated with oral dexamethasone for 3 days, starting 1 day prior to docetaxel administration. Treatment continued until disease progressed or unacceptable toxicity occurred.

Before each 21-day cycle, patients had to have adequate neutrophil and platelet counts as defined by the eligibility criteria, and all non-haematological toxicities (except alopecia) must have subsided to National Cancer Institute Common Toxicities Criteria (CTC) (version 2.0) grade $\leq$1. A cycle could be delayed by up to 8 weeks to allow for recovery from toxicity. Baseline radiological tumour assessments were performed no more than 4 weeks before the first cycle of treatment and were repeated every three cycles.

Patients requiring a dose reduction continued to receive the reduced dose for the remainder of the trial. Treatment was discontinued in any patient with two prior dose reductions who experienced a toxicity that caused a third dose reduction. Toxicities were recorded using CTC, except for hand-and-foot syndrome.

Responses were assessed using the Response Evaluation Criteria in Solid Tumours and were described as either complete responses (CR) or partial responses (PR). Any changes in tumour size had to be confirmed 3–4 weeks after the response criteria for CR or PR were first met.

The duration of overall response was specified as the time between response and objective documentation of recurrent or progressive disease; OS was defined as the time from randomisation to patient death from any cause and PFS was described as the time from randomisation to documented disease progression or death.

It was anticipated that 300 patients would be enrolled over 24 months with an additional 12-month follow-up period. The final analysis was planned to occur after 250 patients had experienced disease progression or had died. This protocol gives an 80% likelihood of detecting a difference in PFS at a 10% significance level if the true hazard ratio is 0.73 (equivalent to an improvement in median PFS from 6 months [capecitabine plus docetaxel] to 8.2 months [gemcitabine plus docetaxel]).

3. Results

The two groups were well balanced in terms of prognostic factors: age, performance status, stage of disease, sites and number of metastases and oestrogen, progesterone and HER2 receptor status. The proportion of patients who had prior therapy was also similar: 69% vs 70% received anthracyclines in a (neo)adjuvant setting; 11% vs 9% received prior taxane therapy; and 14% vs 13% received two lines of cytotoxic chemotherapy in the gemcitabine plus docetaxel and capecitabine plus docetaxel groups, respectively (Table 1). One patient in the capecitabine plus docetaxel group had received no prior cytotoxic chemotherapy.

The efficacy analysis was based on 305 patients randomised on an intention-to-treat basis. Three patients did not participate: one patient died before treatment and two patients withdrew consent. Therefore, the safety analysis was based on the 302 patients treated in the study. An analysis of the study was performed after disease progression had been documented in 259 patients. The results were presented at the ASCO meeting earlier this year [13].

Efficacy results were similar for the two groups: median PFS was 35 weeks for both groups, with median follow-up periods of 88 and 78 weeks in the gemcitabine plus docetaxel and capecitabine plus docetaxel groups, respectively (Table 2, Fig. 1). RR was 32% for both groups, the median duration of response was 36 and 42 weeks, and median TTF was 19 and 18 weeks in the gemcitabine plus docetaxel and capecitabine plus docetaxel arms, respectively (Table 3). Fig. 2 shows the Kaplan-Meier plot of the TTF data.

Patients in the gemcitabine plus docetaxel group received a higher total number of cycles compared with the capecitabine plus docetaxel group: 875 versus 758 cycles, respectively (Table 4). The relative mean dose intensity was

Table 1
Prior therapy

	GD arm (N = 152)	CD arm (N = 150)
Prior adjuvant/neoadjuvant chemotherapy (%)	116 (76)	118 (79)
Anthracycline	105 (69)	105 (70)
Taxane	17 (11)	13 (9)
Prior chemotherapy for metastases (%)	57 (38)	50 (33)
Prior chemotherapy	152 (100)	149 (99)
Adjuvant/neoadjuvant only	95 (63)	99 (66)
Metastases only	36 (24)	31 (21)
Both	21 (14)	19 (13)
Prior hormonal therapy for metastatic disease (%)	63 (41)	51 (34)

GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel.

Table 2
Progression-free survival

	GD arm (N = 153)	CD arm (N = 152)
Events (%)	136 (89)	123 (81)
Median PFS (weeks)	35	35
95% CI	29–37	31–38
Progression free at 6 months (%)	91 (59)	94 (62)
Progression free at 12 months (%)	31 (20)	35 (23)
Median follow-up duration (weeks)	88	78
95% CI	76–99	70–87

GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel; PFS: progression-free survival; CI: confidence interval.

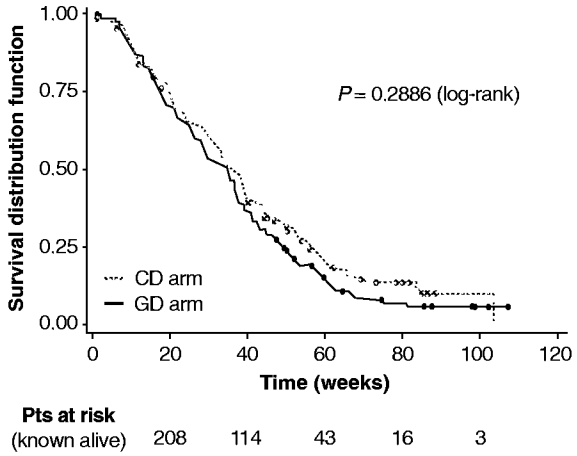

Fig. 1. Progression-free survival. CD: capecitabine plus docetaxel; GD: gemcitabine plus docetaxel; PTS: patients.

Table 3
Efficacy measures

	GD arm (N = 153)	CD arm (N = 152)	P value
ORR [a] (%)	32	32	0.9332
95% CI	24.6–39.4	24.2–39.0	
CR, N (%)	7 (5)	4 (3)	
PR, N (%)	42 (27)	44 (29)	
Median TTF (weeks)	19	18	0.5056
95% CI	18–20	17–19	
Median response duration (weeks)	36	42	0.3131
95% CI	30–42	33–45	

[a] Investigator assessed.
GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel; ORR: overall response rate; CI: confidence interval; CR: complete response; PR: partial response; TTF: time to treatment failure.

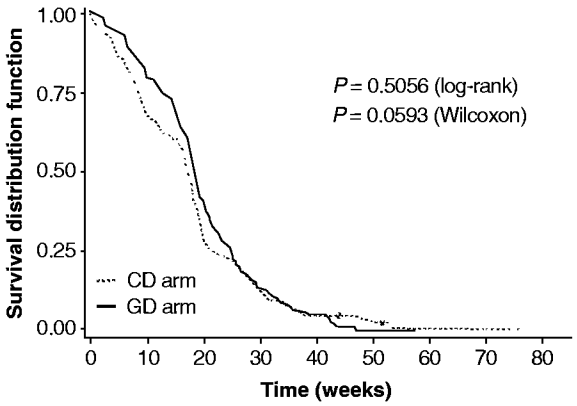

Fig. 2. Time to treatment failure. CD: capecitabine plus docetaxel; GD: gemcitabine plus docetaxel.

Table 4
Dose administration

	GD arm (N = 152)		CD arm (N = 150)	
Number of cycles	875		758	
Median (range)	6 (1–12)		6 (1–15)	
	G	D	C	D
Dose reductions [a], N (%)	228 (26)	62 (7)	223 (29)	83 (11)
Dose delays [b], N (%)	118 (13)	75 (9)	63 (8)	70 (9)
Dose omissions [a], N (%)	262 (30)	1 (<1)	257 (34)	1 (<1)
Dose intensity				
Planned mean dose, mg/m^2/wk	667	25	11,667	25
Acual mean dose, mg/m^2/wk	487	23	6974	23
Relative mean dose intensity (%)	73*	93	60*	93

[a] Primarily due to neutropenia.
[b] Primarily due to scheduling conflict.
* $P < 0.0001$, based on a post-hoc analysis.
GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel.

Table 5
Grade 3/4 haematological toxicity

	GD arm (N = 152)		CD arm (N = 150)	
Toxicity, N (%)	Grade 3	Grade 4	Grade 3	Grade 4
Febrile neutropenia	7 (5)	5 (3)	10 (7)	9 (6)
Neutropenia	45 (30)	84 (55)	37 (25)	86 (57)
Leukopenia	89 (59)	32 (21)	64 (43)	35 (23)
Thrombocytopenia [a]	15 (10)	1 (<1)	3 (2)	2 (1)
Anaemia	6 (4)	5 (3)	3 (2)	1 (<1)

[a] Platelet transfusions for 3 patients in GD and 1 patient in CD.
GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel.

Table 6
Grade 3/4 non-haematological toxicity [a]

	GD arm (N = 152)		CD arm (N = 150)	
Toxicity, N (%)	Grade 3	Grade 4	Grade 3	Grade 4
Hand-and-foot syndrome *	0	0	39 (26)	0
Diarrhoea *	11 (7)	1 (<1)	25 (17)	2 (1)
Mucositis *	6 (4)	0	20 (13)	6 (4)
Nausea/vomiting	13 (9)	0	8 (5)	0
Abdominal pain	1 (<1)	0	5 (3)	0
Asthenia	11 (7)	0	16 (11)	0
Alopecia	12 (8)	0	11 (7)	0
Fatigue	6 (4)	0	4 (3)	0
Myalgia	5 (3)	1 (<1)	3 (2)	1 (<1)
AST/ALT	12 (8)	0	7 (5)	0
Alkaline phosphatase	5 (3)	0	3 (2)	0

[a] Toxicities <3% in either arm were not included.
* Statistically significant between arms; respiratory toxicities were rare and not statistically significant between arms.
GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel.

higher for gemcitabine plus docetaxel (73%) compared with capecitabine plus docetaxel (60%; $P < 0.0001$).

Grade 3/4 haematological toxicities are shown in Table 5. No significant difference was seen for febrile neutropenia (8% vs 13%) or neutropenia (85% vs 82%) for gemcitabine plus docetaxel and capecitabine plus docetaxel, respectively.

Table 7
Overall safety (1)

	GD arm (N = 152)	CD arm (N = 150)
Serious adverse events, N (%)		
All events	46 (30)	57 (38)
Drug-related events	36 (24)	39 (26)
Discontinuations due to AEs, N (%)		
All events	22 (14)	45 (30)
Drug-related events [a]	20 (13)	42 (28)
Deaths (on study/30-day follow up), N (%)		
All events	4 (3)	5 (3)
Drug-related events	0	2 (1)
Progressive disease	2 (1)	3 (2)

[a] $P = 0.0014$, based on a post-hoc analysis; two non-drug related events in the GD arm.
GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel; AEs: adverse events.

Table 8
Overall safety (2)

	GD arm (N = 152)	CD arm (N = 150)
Discontinuations due to drug-related AEs, N (%)	20 (13)	42 (28)
Hand-and-foot syndrome	1 (<1)	14 (9)
Mucositis	0	3 (2)
Abdominal pain	0	2 (1)
Diarrhoea	0	2 (1)
Peripheral neuropathy	2 (1)	1 (<1)
Neutropenia	2 (1)	7 (5)
Leukopenia	0	3 (2)
Other (<1% in either arm) [a]	15 (10)	10 (7)

[a] Includes nausea, vomiting, paralytic ileus, asthenia, fatigue, oedema, infection, recall phenomenon, elevated ALT, myalgia, dizziness, neurotoxicity, depression, dyspnoea, lung disorder, pneumonia aspiration, nail disorder, skin eruption and lymphoedema.
GD: gemcitabine plus docetaxel; CD: capecitabine plus docetaxel; AEs: adverse events.

Non-haematological toxicity profiles of the two combinations are summarised in Table 6. Lower incidences of hand-and-foot syndrome (0% vs 26%), grade 3/4 diarrhoea (7–8% vs 18%) and grade 3/4 mucositis (4% vs 17%) were seen in the gemcitabine plus docetaxel arm.

The incidence of serious adverse events was similar in each group. However, adverse events (AEs) leading to treatment discontinuation were twice as likely to occur in the capecitabine plus docetaxel group (28%) compared with the gemcitabine plus docetaxel group (13%; Tables 7 and 8). Treatment discontinuation due to drug-related AEs in the capecitabine plus docetaxel group was most commonly related to toxicities (Table 8).

4. Conclusions

The doses of docetaxel and capecitabine used were based on a large Phase III study, which resulted in FDA approval

of capecitabine for the treatment of advanced breast cancer [5]. Two retrospective studies of these data have shown that a 25% reduction in capecitabine dose results in a similar response rate to that achieved with the full dose [14,15]. However, the assumption that the lower dose has the same efficacy to the standard dose remains speculative.

The dose of gemcitabine selected for the study was based on data collected from Phase II studies, where it proved to be safe and effective in this patient population [6–11]. A recent Phase III study comparing gemcitabine plus paclitaxel with single-agent paclitaxel showed similar efficacy to the gemcitabine plus docetaxel combination investigated in this trial [12]. The similar efficacy at a lower gemcitabine dose in the gemcitabine plus docetaxel combination may be explained by a greater synergistic effect of gemcitabine plus docetaxel compared with gemcitabine plus paclitaxel. Alternatively, the lower dose of gemcitabine may compensate for greater myelotoxicity of docetaxel.

Results from this Phase III study showed that gemcitabine plus docetaxel has a better toxicity profile compared with capecitabine plus docetaxel in terms of hand-and-foot syndrome, diarrhoea and mucositis. In fact, patients in the gemcitabine plus docetaxel arm experienced fewer treatment discontinuations due to side-effects. The comparison of efficacy parameters showed the combinations to be similar in terms of PFS, ORR and TTF. This Phase III study has also provided further evidence that combination therapy offers a survival advantage compared with single-agent therapy [12]. Furthermore, it demonstrated that the addition of gemcitabine to docetaxel is well tolerated.

5. Summary

Although these trials provide clear evidence that combination therapy offers a survival advantage compared with single-agent treatments, the relative merits of sequential versus combination therapy with these agents has not been addressed [5,12]. In a three-arm trial, MBC patients received either doxorubicin followed at disease progression by paclitaxel, paclitaxel followed at disease progression by doxorubicin or a combination therapy of doxorubicin plus paclitaxel [16]. Efficacy was similar in the two sequential arms. The combination arm was superior in terms of ORR and TTF, but these results did not translate into a significant survival advantage.

Nevertheless, in a young and fit patient with urgent symptoms due to MBC, combination therapy is the preferred treatment option. This Phase III study has provided evidence that the combination of gemcitabine and docetaxel is an effective and safe treatment for anthracycline-pretreated MBC patients.

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