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Docetaxel versus docetaxel alternating with gemcitabine as treatments of advanced breast cancer: final analysis of a randomised trial

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Background: Alternating administration of docetaxel and gemcitabine might result in improved time-to-treatment failure (TTF) and fewer adverse events compared with single-agent docetaxel as treatment of advanced breast cancer.
Patients and methods: Women diagnosed with advanced breast cancer were randomly allocated to receive 3-weekly docetaxel (group D) or 3-weekly docetaxel alternating with 3-weekly gemcitabine (group D/G) until treatment failure as first-line chemotherapy. The primary end point was TTF.
Results: Two hundred and thirty-seven subjects were assigned to treatment (group D, 115; group D/G, 122). The median TTF was 5.6 and 6.2 months in groups D and D/G, respectively (hazard ratio 0.85, 95% confidence interval 0.63–1.16; $P = 0.31$). There was no significant difference in time-to-disease progression, survival, and response rate between the groups. When adverse events were evaluated for the worst toxicity encountered during treatment, there was little difference between the groups, but when they were assessed per cycle, alternating treatment was associated with fewer severe (grade 3 or 4) adverse effects ($P = 0.013$), and the difference was highly significant for cycles when gemcitabine was administered in group D/G ($P < 0.001$).
Conclusion: The alternating regimen was associated with a similar TTF as single-agent docetaxel but with fewer adverse effects during gemcitabine cycles.
Key words: advanced stage, breast cancer, chemotherapy, docetaxel, gemcitabine, randomised clinical trial

introduction

Taxanes are effective in the treatment of advanced breast cancer [1–3]. For docetaxel, response rates range from 34% to 64%, and time-to-disease progression (TTP) is ~6 months as first-line treatment [4–7].

Docetaxel administration not infrequently causes adverse effects that may result in treatment discontinuation before cancer progression [2, 5]. We hypothesised that alternating docetaxel administration with a chemotherapy agent that has a different side-effect profile might result in a longer time-to-treatment failure (TTF) than docetaxel monotherapy, and such therapy might cause fewer adverse effects. We selected gemcitabine as the agent to be alternated with docetaxel because gemcitabine is relatively well tolerated and has activity as monotherapy for advanced breast cancer [8, 9]. Efficacy of gemcitabine combined with either paclitaxel or docetaxel compares well with taxane monotherapy as first-line treatment of advanced breast cancer [10, 11].

In the present study, we compared docetaxel monotherapy with a regimen where docetaxel is alternated with gemcitabine (D-G-D-G-D-G…) as first-line treatments for advanced breast cancer. To our knowledge, a similar trial has not been conducted earlier.

patients and methods

study population

Women aged 70 years or younger with histologically confirmed invasive breast carcinoma were eligible, provided that they had measurable or non-measurable distant metastases confirmed histologically and/or radiologically. Adjuvant chemotherapy, administered with or without taxanes, was required to have been completed ≥6 months before enrolment. Staging work-up included computed tomography or magnetic resonance

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imaging with or without chest radiography, an electrocardiogram, and analysis of blood cell counts and blood biochemistry.

Exclusion criteria included prior chemotherapy for metastatic disease, World Health Organization (WHO) performance status (PS) of more than two, history of cancer other than breast cancer, and any medical condition that precluded administration of chemotherapy. Subjects with ascites or pleural effusion as the sole manifestation of the disease and those with brain or leptomeningeal metastases were excluded, as well as subjects with metastatic lesions assessable by radionuclide scan only or with sclerotic bone lesions as the only manifestation of the disease. Patients with impaired liver function [serum bilirubin >1.5 ×N (times normal), alanine or aspartate aminotransferase >3.0 ×N, alkaline phosphatase >5.0 ×N except in the presence of bone disease and in absence of liver disorder] were not eligible nor were those who had impaired renal function (serum creatinine >1.5 × N), the blood neutrophil count <1.5 × 10^9/ml, platelet count <100 × 10^9/ml, or haemoglobin level <100 g/l.

The study protocol (ClinicalTrials.gov identifier NCT00191243) was approved by an institutional ethics committee. Study participants provided a written informed consent before entry.

treatments

The participants were randomly assigned (centrally with computer concealing) to a study group in this open, prospective, phase III, multicentre trial. At random assignment, the subjects were stratified according to WHO PS (0 or 1 versus 2), prior exposure to taxanes in the adjuvant setting, and the participating institution, and were allocated in a 1:1 ratio to receive either docetaxel (Taxotere, Sanofi-Aventis, Paris, France) (group D) or docetaxel alternating with gemcitabine (Gemzar, Eli Lilly, IN) (group D/G). Docetaxel, administered intravenously 100 mg/m^2 over 60 min, was given on day 1 of a 21-day cycle in both groups. Gemcitabine 1000 mg/m^2 was administered as a 30- to 60-min intravenous infusion on days 1 and 8 of a 21-day cycle in group D/G. Following study protocol amendment (9 January 2003), the docetaxel starting dose was reduced to 80 mg/m^2 in both groups to reduce the risk of neutropenic infections. The number of chemotherapy cycles administered was not limited.

Dexamethasone was given at times of docetaxel administration. Prophylactic antibiotics or granulocyte colony-stimulating factors were not recommended unless one or more episodes of febrile neutropenia or severe infection occurred. Administration of trastuzumab at the standard dosing was allowed for HER2-positive cancer [7, 12] and bisphosphonates and palliative radiation therapy for patients with bone metastases.

After treatment failure, the scheduled second-line systemic therapy in group D was single-agent gemcitabine administered as described above. Second-line therapy was not defined for patients assigned to the alternating therapy. Selection of the later lines of therapy was at the discretion of the treating physician. After completion of the protocol treatments, the study participants were followed up at ∼3-month intervals until death or for a minimum time period of 2 years.

study procedures

Blood cell counts and biochemistry were analysed before each cycle and blood cell counts on cycle day 8. Adverse effects were graded according to the National Cancer Institute Common Toxicity Criteria version 2.0 (http://ctep.cancer.gov/reporting/ctc.html) and were collected on structured forms on day 21 of each cycle. Tumour imaging was carried out at every third cycle. Response to treatment was assessed during the study and centrally at the completion of the study according to the RECIST criteria [13].

Chemotherapy doses were reduced when a nadir neutrophil count <0.5 × 10^9/l persisted for ≥7 days or when febrile neutropenia occurred (fever ≥38.0 associated with neutrophil count <1.0 × 10^9/l). Docetaxel dose was not reduced <60 mg/m^2. Whenever haematological recovery did not take place before the next cycle was scheduled to begin, blood cell counts were repeated weekly until the neutrophil count was ≥1.5 × 10^9/l and the platelet count ≥100 × 10^9/l.

Treatment was considered to have failed when haematological recovery did not take place within 6 weeks from day 1 of the prior chemotherapy cycle, a nadir neutrophil count <0.5 × 10^9/l persisted for >7 days, febrile neutropenia occurred at the docetaxel dose level of 60 mg/m^2, non-haematological toxicity did not resolve to grade <3 within 3 weeks, in case of anaphylaxis or fluid retention of grade ≥3, or any treatment break exceeded 6 weeks.

statistical analysis

TTF was preferred to TTP as the primary end point to account for both unsatisfactory treatment efficacy and toxicity as potential causes of treatment failure. Disease progression, unacceptable toxicity, death, or discontinuation of chemotherapy from any cause were considered treatment failures. Secondary end points included response rate, response duration, survival, treatment safety, and TTP.

The sample size (120 patients per group) was calculated assuming that TTF, calculated from the date of initiation of chemotherapy to the date of treatment failure, will be 20 and 36 weeks in groups D and D/G, respectively, assuming a power of 0.80 and a significance level of 0.05.

TTP was measured from the date of initiation of chemotherapy until the date of progressive disease (PD) or death (whichever occurred first) and survival to the date of death. Duration of complete response (CR) and partial response (PR) was measured from the date when CR or PR was documented until the date of first disease progression.

Frequency tables were analysed using the chi-square test or Fisher's exact test. Survival between groups was compared using the Kaplan–Meier life-table method and the Cox proportional hazards model; the log-rank test was used to confirm effect consistency. Efficacy analyses were based on the intention-to-treat-principle. Subjects who received at least one cycle of chemotherapy were included in safety analyses and those who received ≥2 cycles for analysis of the response rate. When adverse events were evaluated per cycle, a generalised estimating equations model for repeated measurements was used [14]. The binary responses (event versus no event) at each cycle were used as dependent variables, and the treatment group, chemotherapy cycle, and the interaction between the treatment group and the cycle were used as explanatory variables in the model. The analysis was carried out with the GENMOD procedure of the SAS System. *P* values are two-sided.

results

patient characteristics

Between 14 March 2002 and 20 September 2006, 240 subjects were entered. Two hundred and thirty-seven subjects were assigned to treatment: 115 to receive single-agent docetaxel (group D) and 122 to docetaxel alternating with gemcitabine (group D/G, Figure 1). One patient who did not receive the first chemotherapy dose was excluded from the efficacy analyses (group D). The allocation groups were balanced with respect of the characteristics examined (Table 1).

treatment

A median of 8.0 chemotherapy cycles were administered in both groups before treatment failure (range, 1 to 28). Thirty-seven (82%) of the 45 patients assigned to a docetaxel starting dose of 100 mg/m^2 had dose reduced during treatment

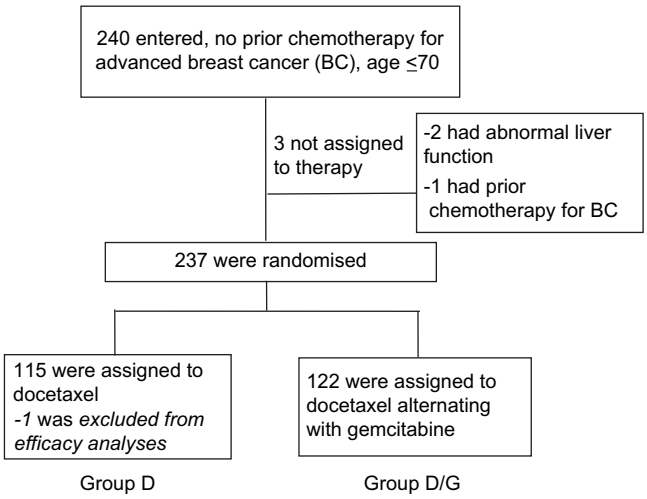

Figure 1. The Consolidated Standards of Reporting Trials diagram of the study.

(group D, 19 out of 22; group D/G, 18 out of 23) compared with 106 (55%) of the 192 patients assigned to receive 80 mg/m^2 following study protocol amendment (group D, 54 out of 93; group D/G, 52 out of 99; $P = 0.0009$).

The mean docetaxel doses administered per cycle were similar between the groups. The mean doses of gemcitabine administered ranged from 919 to 952 mg/m^2. The most common reasons for dose reduction were neutropenia and neutropenic infections. Twenty-one (78%) of the 27 patients with HER2-positive cancer assigned to group D and 15 (65%) of 23 such patients assigned to group D/G received trastuzumab ($P = 0.32$).

efficacy

The median follow-up time of the patients alive after randomisation was 25 months on the date of database closure on 15 May 2007 when the follow-up time of the last patient entered exceeded 28 weeks. A total of 166 (70%) subjects had failed treatment [group D, 85 (74%); group D/G, 81 (66%)], the most common reasons being an adverse event [group D, $n = 46$ (54%); group D/G, $n = 35$ (43%)] and progressive cancer [group D, $n = 34$ (40%); group D/G, $n = 36$ (44%)].

The median TTF was 5.6 and 6.2 months in groups D and D/G, respectively [hazard ratio (HR) 0.85, 95% confidence interval (CI) 0.63–1.16; $P = 0.31$], and similarly, TTP did not differ significantly between the groups (median, 11.7 versus 11.3 months, respectively; HR 1.05, 95% CI 0.79–1.41; $P = 0.72$). There was no difference in overall survival between the groups (101 patients died; group D median, 28 months; group D/G, 27 months; HR 1.11, 95% CI 0.75–1.64; $P = 0.60$; Figure 2). Exploratory analyses of TTF stratified by WHO PS, prior exposure to taxanes in the adjuvant setting, and HER2 expression indicated presence of no difference in TTF between the treatments in these subgroups (supplemental Figure S1, available at *Annals of Oncology* online).

Six (6%) patients in group D and 10 (9%) in group D/G achieved CR as their best response, 63 (59%) and 57 (50%) PR, 27 (25%) and 38 (33%) stable disease (SD), and 10 (9%) and 10 (9%) PD, respectively. At central evaluation, 13% and 10%

Table 1. Patient and tumour characteristics at baseline

Characteristic	Docetaxel ($n = 115$)	Docetaxel alternating with gemcitabine ($n = 122$)	Total ($N = 237$)
Patient characteristics			
Age, years			
Median	55	54	55
Range	31–69	32–70	31–70
Time from primary diagnosis to randomisation, years			
Median	5.0	3.4	4.0
Range	0.0–24.7	0.0–25.8	0.0–25.8
Time from first diagnosis of distant metastases to randomisation, years			
Median	0.1	0.1	0.1
Range	0.0–5.2	0.0–12.6	0.0–12.6
WHO performance status, *n* (%)			
0	36 (31)	40 (33)	76 (32)
1	72 (63)	72 (59)	144 (61)
2	6 (5)	9 (7)	15 (6)
N.A.	1 (1)	1 (1)	2 (1)
Site of metastatic disease, *n* (%)			
Bone	75 (65)	71 (58)	146 (62)
Liver	50 (44)	56 (46)	106 (45)
Lymph	44 (38)	40 (33)	84 (35)
Lung	39 (34)	39 (32)	78 (33)
Pleura	23 (20)	19 (16)	42 (18)
Skin	18 (16)	14 (12)	32 (14)
Other	17 (15)	15 (12)	32 (14)
Adjuvant chemotherapy, *n* (%)			
Yes	61 (53)	70 (57)	131 (55)
No	54 (47)	52 (43)	106 (45)
Taxane as adjuvant chemotherapy, *n* (%)			
Yes	7 (6)	14 (11)	21 (9)
No	108 (94)	108 (89)	216 (91)
Hormonal therapy before study entry[a], *n* (%)			
Yes	67 (58)	64 (52)	131 (55)
No	48 (42)	58 (48)	106 (45)
Primary tumour characteristics			
Histopathological type, *n* (%)			
Ductal	90 (78)	87 (71)	177 (75)
Lobular	19 (17)	27 (22)	46 (19)
Other	5 (4)	6 (5)	11 (5)
N.A.	1 (1)	2 (2)	3 (1)
Histological grade, *n* (%)			
Grade 1	12 (10)	12 (10)	24 (10)
Grade 2	47 (41)	53 (43)	100 (42)
Grade 3	45 (39)	42 (34)	87 (37)
N.A.	11 (10)	15 (12)	26 (11)
ER, *n* (%)			
Positive	82 (71)	90 (74)	172 (73)
Negative	29 (25)	32 (26)	61 (26)
N.A.	4 (4)	0 (0)	4 (2)
PR, *n* (%)			
Positive	67 (58)	80 (66)	147 (62)
Negative	43 (37)	42 (34)	85 (36)
N.A.	5 (4)	0 (0)	5 (2)
HER-2, *n* (%)			
Positive	27 (24)	23 (19)	50 (21)
Negative	66 (57)	86 (71)	152 (64)
N.A.	22 (19)	13 (11)	35 (15)

[a]Includes hormonal therapy administered in the adjuvant setting and/or for advanced disease

WHO, World Health Organization; N.A., not available; ER, estrogen receptor; PR, progesterone receptor; HER-2, erbB2 tyrosine kinase receptor [positive: either immunohistochemistry strongly positive (+++) or an *in situ* hybridisation test positive].

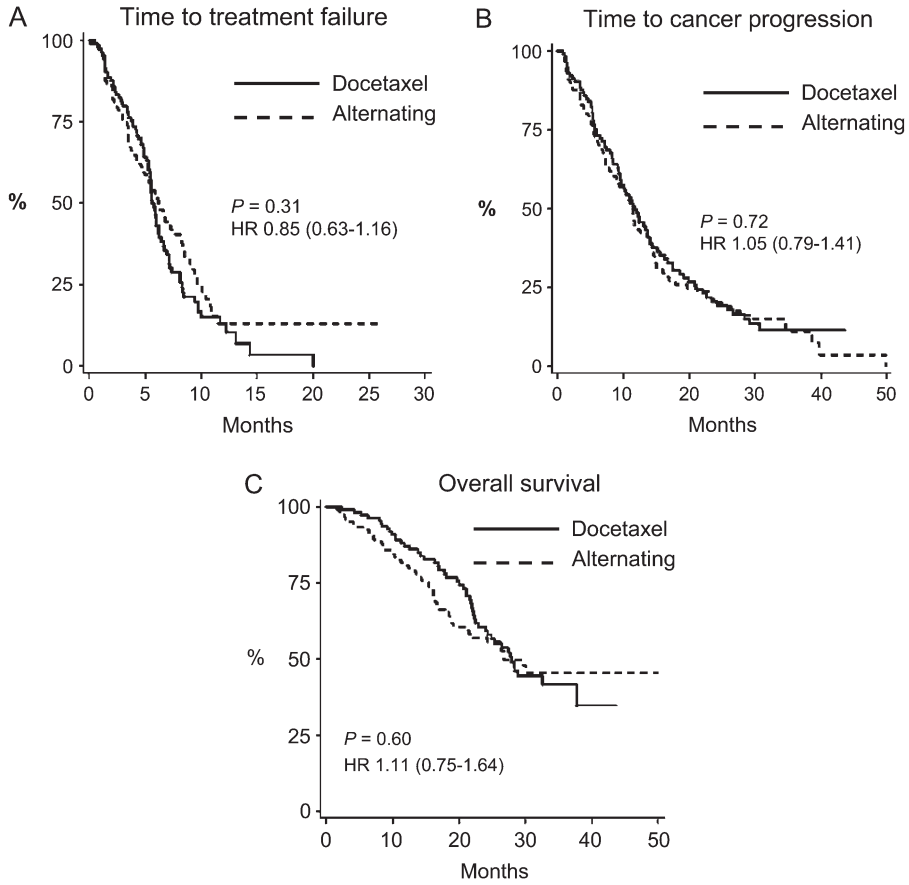

Figure 2. Time-to-treatment failure (A), time-to-disease progression (B), and overall survival (C).

of the patients in groups D and D/G, respectively, achieved CR, 71% and 65% PR, 13% and 22% SD, and 3% and 3% PD. The objective response rate (CR + PR) did not differ between groups D and D/G, regardless of whether it was assessed by in-house investigators (65% versus 58%, respectively; $P = 0.30$) or centrally (84% versus 75%; $P = 0.15$). The duration of objective response did not differ between the groups (D, 10.9 months versus D/G, 12.9 months; HR 0.85, 95% CI 0.57–1.28; $P = 0.44$).

treatment tolerability

Grade 3 or 4 haematological adverse effects occurred in 99% and 96% of patients allocated to group D and D/G, respectively ($P = 0.21$), and 61% and 55% had grade 3 or 4 non-haematological adverse events ($P = 0.34$). Patients allocated to docetaxel had more frequently grade 3 or 4 dyspnoea (21%) than those allocated to alternating chemotherapy (10%; $P = 0.015$; Table 2). One chemotherapy-related death was recorded in group D.

When adverse events were evaluated per cycle instead of assessing the worst toxicity encountered during the entire treatments, alternating treatment was associated with fewer severe adverse effects ($P = 0.013$; amenorrhoea was excluded from the analyses). The difference was highly significant for even-numbered cycles (when gemcitabine was administered in group D/G; $P < 0.001$) but not for odd-numbered cycles (when docetaxel was administered in both groups; $P = 0.09$). Both severe haematological and non-haematological adverse effects were less in group D/G during gemcitabine cycles.

second-line gemcitabine

Forty-five (39%) subjects assigned to group D received gemcitabine as second-line treatment. Five (11%) of the 44 assessable patients achieved a PR. Thirteen (30%) failed due to adverse events (most commonly infection) and 14 (32%) due to PD; 17 had gemcitabine discontinued at PR or SD after a median of 5.5 months of treatment.

discussion

The study failed to demonstrate that alternating two single-agents (docetaxel and gemcitabine) with different toxicity profiles leads to a longer TTF than administration of docetaxel alone. Patients who received the alternating therapy had a similar frequency of serious adverse events as those who received docetaxel when the worst toxicity encountered during the entire treatment was considered, but they had fewer serious events when toxicity was analysed per cycle of chemotherapy administered.

Regimens where single-agent taxane is alternated with another single-agent [15, 16] or combination therapy [17] have rarely been evaluated as treatments of advanced breast cancer. Two prospective randomised trials have compared docetaxel alternating with doxorubicin to the same agents administered in a sequence [15, 16]. Both trials differed from the present study in several key aspects: the number of chemotherapy cycles was limited to a maximum of eight, the primary end point

Table 2. Recorded adverse events[a]

	Docetaxel		Docetaxel/gemcitabine		P^b
	Grade 1/2 (%)	Grade 3/4[c] (%)	Grade 1/2 (%)	Grade 3/4 (%)	
Haematological					
Neutropenia	0.9	99.1	3.3	95.9	0.21
Leukopenia	11.5	86.7	14.8	84.4	0.62
Anaemia	69.9	0.9	81.1	0.0	0.48
Thrombocytopenia	16.8	0.0	35.2	4.1	0.061
Febrile neutropenia	0.0	27.4	0.0	32.0	0.45
Non-haematological					
Irregular or absent menstrual cycle	0.9	98.2	5.7	92.6	0.061
Fatigue	74.3	23.9	77.0	20.5	0.53
Dyspnoea	49.6	21.2	45.9	9.8	0.015
Myalgia	68.1	15.0	72.1	10.7	0.31
Pain	66.4	14.2	68.0	14.8	0.90
Infection, no neutropenia	46.9	11.5	36.1	19.7	0.086
Diarrhoea	62.8	5.3	68.0	1.6	0.16
Oedema	69.9	5.3	66.4	1.6	0.16
Nausea	53.1	4.4	73.8	4.1	0.90
Vomiting	32.7	3.5	29.5	5.7	0.54
Other	73.0	27.0	77.4	22.6	0.59

[a]At least one completed toxicity evaluation form was required for subject inclusion in the safety analysis (235 cases were included). The adverse events are presented by the worst grade of severity encountered during the study.
[b]*P* values denote comparison between grade 3 to 4 adverse events between the groups.
[c]One fatal (grade 5) adverse event was recorded in the docetaxel arm.

was the CR rate, and the numbers of subjects in these trials were small. Both trials found no significant difference in the CR rates (range, from 2% to 14%), response rates (range, from 52% to 67%) and the TTP (range, from 7.6 to 9.0 months) between the alternating and the sequential treatments.

The present study has some limitations. A clinically significant difference in the TTF might have been missed due to the study size. Yet, we found no trend in the TTF in favour of either treatment with the current sample size indicating that the size of the undetected difference, if any, is likely small. We did not assess quality of life, which might have differed between the groups. The study protocol recommended single-agent gemcitabine as the second-line treatment following docetaxel failure in group D, but only 39% of these patients received it probably due to investigator preference to administer other agents following taxane failure.

We conclude that alternating administration of docetaxel with gemcitabine as first-line systemic chemotherapy for metastatic breast cancer did not result in a longer TTF compared with single-agent docetaxel, but adverse effects were generally fewer during the gemcitabine cycles.

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disclosure

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