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ORIGINAL ARTICLE

A randomized, placebo-controlled, double-blind phase 2 study of docetaxel compared to docetaxel plus zosuquidar (LY335979) in women with metastatic or locally recurrent breast cancer who have received one prior chemotherapy regimen

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Abstract
Purpose To determine if concomitant administration of docetaxel plus zosuquidar.3HC1 can prolong progression-free survival in patients with metastatic breast cancer.
Methods A randomized, double-blind, multicenter, placebo-controlled clinical trial comparing docetaxel plus 500 mg zosuquidar.3HCl (DZ) with docetaxel plus placebo (DP).
Results A total of 170 patients were enrolled and randomly assigned to treatment. The median age was 53 years (range, 31–74 years). 81.7% of patients had prior chemotherapy in the adjuvant setting and 18.3% in the neoadjuvant setting. The median progression-free survival time was statistically different between groups [7.2 months (DZ) vs. 8.3 months (DP)]. Once the stratification factor relative to progression following prior chemotherapy was considered, no significant treatment difference existed.
Conclusion The combination of zosuquidar.3HCl plus docetaxel is safe. The analysis of efficacy data is complex, but it can be concluded that there is no difference in progression-free survival, overall survival, or response rate in the study as a whole.

Keywords Zosuquidar · Metastatic · Breast cancer · Docetaxel

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Introduction

Breast cancer is the most commonly diagnosed form of cancer and is the second most common cause of cancer-related death in women, both in Europe and in the USA. It was estimated that in the year 2005 about 40,410 patients would die from metastatic breast carcinoma in the USA [1, 2]. A meta-analysis of over 75,000 patients has shown that in selected subgroups of patients, chemotherapy given in the adjuvant setting can yield meaningful improvements in both progression free survival and overall survival [3]. Unfortunately, a large proportion of patients develop metastatic disease and require chemotherapy to palliate symptoms, improve quality of life and prolong survival [4].

At the time this study was developed, the anthracyclines were among the most active agents used in the treatment of advanced breast cancer [5]. Historically there had been no

standard chemotherapy for second or third line disease. Current agents were yielding response rates in the region of 7–40%, with the outcome being even more dismal in patients with anthracycline refractory or resistant disease [6]. The advent of the taxanes, paclitaxel and docetaxel provided useful alternatives in this setting with larger increases in response rates being reported [7]. Docetaxel produced the highest recorded response rates in anthracycline- or anthracenedione-resistant disease [8, 9]. However, despite these advances, the majority of patients with metastatic breast cancer will still develop resistance to the anthracyclines and taxanes and ultimately die with progressive, resistant disease.

A major obstacle to improving treatment outcomes in clinical oncology is tumour resistance to chemotherapeutic agents; the expression of P-glycoprotein (gp 170; encoded by the MDR1 gene) in breast cancer tumours has been demonstrated to be associated with a poor response to chemotherapy. The proportion of breast tumours expressing MDR1/gp170 was shown to be 41.2% but there was substantial heterogeneity in the values across individual studies; an increase in the proportion of tumours expressing MDR1/gp170 have been associated with chemotherapeutic drugs and/or hormonal agents. Patients with tumours expressing MDR1/gp170 are three times more likely to fail to respond to chemotherapy than patients whose tumours are MDR1/gp170 negative (RR = 3.21; 95%; 95% CI = 2.28–4.51); this relative risk increased to 4.19 (95% CI = 2.71–6.47) when considering only patients whose tumour expression of MDR1/gp170 was measured after chemotherapy [10].

Zosuquidar.3HC1 is one of the most active modulators of p-glycoprotein (P-gp), demonstrating potent in vitro (K_i = 59 nM) reversal activity against multidrug resistant human tumour cell lines [11]. It has also demonstrated excellent in vivo activity in preclinical animal studies. In addition, there is an apparent lack of pharmacokinetic interaction between zosuquidar.3HC1 and the cytotoxic compound that is being administered. The 500-mg zosuquidar.3HCl dose was chosen because results from studies with isolated human liver microsomes suggested that potentially significant inhibition of the cytochrome P450 isoenzyme CYP3A would occur at zosuquidar.3HCl concentrations of 4,000 nM and higher. The plasma should optimally stay below 4,000 nM to avoid potential P450 interactions but achieve levels of 500–1,000 nM (approximately 5- to 10-fold higher than the in vitro concentration needed to achieve full-modulating activity). The 500-mg dose level was expected to achieve plasma concentrations of approximately 1,000 nM. Flat dosing was chosen over dosing by body surface area (BSA) because data generated before the start of this study did not suggest a benefit to dosing zosuquidar.3HCl based on BSA.

Thus, there is a strong rationale for examining the combination of zosuquidar.3HC1 and docetaxel in previously treated breast cancer.

Objectives

Primary objective

The primary objective of this study is to determine if first line concomitant administration of docetaxel plus zosuquidar.3HC1 can prolong progression-free survival compared to docetaxel plus placebo in women with metastatic or locally recurrent breast cancer who have previously received one chemotherapy regimen in the neoadjuvant or adjuvant setting.

Secondary objectives

The secondary objectives of this study are to: (a) measure and compare overall survival, time to treatment failure, response rate, and response duration in the two arms; and (b) characterise and compare the toxicities of docetaxel plus zosuquidar.3HC1 to docetaxel plus placebo.

Methods

Study design

This was a randomized, double-blind, multicenter, placebo-controlled clinical trial comparing docetaxel plus zosuquidar.3HCl (DZ) with docetaxel plus placebo (DP) in the treatment of patients with metastatic or locally recurrent breast cancer. To be included in the study, patients had to be women at least 18 years of age with a documented diagnosis of histologic or cytologic metastatic or locally advanced breast cancer. Lesions should not have been amenable to surgery or radiation therapy of a curative intent. Patients also had to have bidimensionally measurable disease, adequate organ function, an estimated life expectancy of at least 12 weeks, and an Eastern Cooperative Oncology Group (ECOG) performance status of 0–2. Additionally, patients should have had prior exposure to one chemotherapy regimen in either the neoadjuvant or adjuvant settings. Patients were stratified according to whether or not they received prior anthracycline therapy and according to disease progression with prior neoadjuvant or adjuvant chemotherapy. Patients were accrued over 24 months.

Patients were to remain on study for six cycles and could receive additional treatment cycles, if both the Lilly clinical research physician and investigator felt that it was in their best interest.

Drug formulation and administration

Beginning on day 1 of cycle 1, patients received either 500 mg of zosuquidar.3HCl or placebo. Zosuquidar.3HCl was supplied as capsules containing either 50 or 200 mg of active drug for oral consumption. The placebo capsules appeared identical to the zosuquidar.3HCl capsules and were administered in the same manner as zosuquidar.3HCl. The drug product was stored at room temperature.

Additionally, beginning on day 1 of cycle 1 and 2 h after the first dose of zosuquidar.3HCl or placebo, all patients received 100 mg/m^2 docetaxel administered over approximately 1 h (acceptable range, 45 min to 1 h and 15 min) as an intravenous infusion. This dose, 100 mg/m^2, is the standard label dose for docetaxel.

Statistical methods

The final analysis was planned to occur after 150 patients had progressed or died. This gave an 80% chance of detecting a difference in progression-free survival (PFS) at the 10% significance level if the true hazard ratio was 0.667 (equivalent to an improvement from 7 months median PFS on docetaxel plus placebo to 10.5 months median PFS on docetaxel plus LY335979).

Estimates of PFS, including medians and confidence intervals, were calculated using the Kaplan–Meier (1958) method. The proportion of patients who were alive and progression free at 12 months was derived for each treatment from these estimates and was reported together with corresponding confidence intervals. A comparison of progression-free survival between treatment groups was conducted using the log-rank test. To assess the impact of the stratification factors, a stratified test was used. Additional exploratory analyses were conducted to better understand which variables were having a significant impact on PFS. In particular, the impact of time to relapse after prior chemotherapy and indicators of disease status at baseline such as diagnosis, histopathological grading, disease stage, progesterone and estrogen receptor status, menopausal status, metastasis presence, and performance status were investigated using log-rank tests.

Overall survival, time-to-treatment failure, and duration of response were also analyzed with log-rank tests. Response rates and corresponding confidence intervals were presented as a proportion of all patients enrolled. The confidence intervals were calculated using the normal approximation to the binomial distribution. A comparison of response rates between treatment groups was conducted using Pearson's Chi squared test. To better understand the effect of zosuquidar.3HCl on hematological parameters, the nadir counts for white blood cells (WBC), neutrophils, platelets, and lymphocytes at cycles 1, 2, and 3 were analyzed. The raw data were log-transformed before analysis because the data on this scale better satisfy the assumptions behind the analysis. The data for all variables were analyzed using a mixed effect model. This technique accounted for any incomplete data and repeated measures on each patient. Least square (LS) means and ratio of LS means were calculated for each treatment group. The planned statistical methods for the primary and secondary endpoints were not changed, but additional analyses were performed to gain a deeper understanding of the data.

A P value <0.01 was considered statistically significant in this study.

Results

Study population

One hundred eighty-four female patients signed an informed consent document and entered into the study. Fourteen patients failed to meet the inclusion criteria for enrollment into the study. A total of 170 patients were thus enrolled into the study and randomly assigned to treatment; one of these patients never received study drugs. The majority of patients enrolled were Caucasian (n = 145, 85.8%), with a median age of 53 years (range, 31–74 years). The most common reasons for study discontinuation were: protocol completion (48.9%), progressive disease (17.9%), and adverse events (9.2%). Most patients had an ECOG performance status of either 0 (62.7%) or 1 (34.9%). All patients had prior chemotherapy: 81.7% of patients had prior chemotherapy in the adjuvant setting and 18.3% in the neoadjuvant setting. Additionally, 69.2% of all patients had prior radiotherapy and 57.4% had prior hormonal therapy. One hundred sixty-six patients had one or more prior surgeries. Of those 166 patients, 94.6% had surgery with a curative intent, 13.3% had surgery with a diagnostic intent, and 4.2% had surgery with a palliative intent.

Primary efficacy results

On the DZ arm, 68 patients either progressed or died, resulting in an 18.1% censoring rate. On the DP arm, 70 patients either progressed or died, resulting in a similar censoring rate of 18.6%. The median progression-free survival time was 7.2 months (95% CI, 5.6–9.0) for patients on the DZ arm and 8.3 months (95% CI, 6.2–10.3) for patients on the DP arm. The difference between the treatment groups was statistically significant at the 10% level in favor of the DP arm. However, once the influence of the stratification factor relative to progression following prior chemotherapy was taken into account, no significant treatment difference existed. These results are shown in Fig. 1.

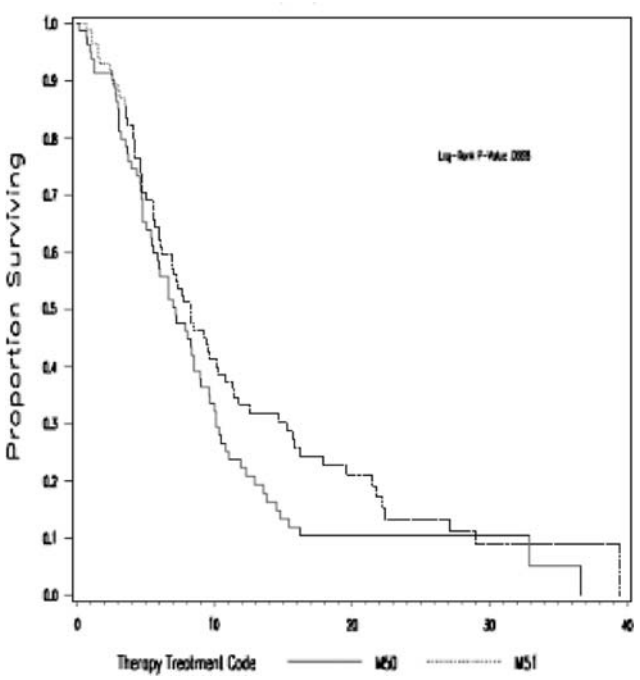

Fig. 1 Kaplan–Meier curve, progression-free survival

Secondary efficacy results

Response

All 169 randomized patients who received study drug qualified for the analysis of tumor response. On the DZ arm, 4 patients had complete responses and 31 patients had partial responses, resulting in a 42.2% response rate (95% CI, 31.5–52.8). On the DP arm, 1 patient had a complete response and 33 patients had partial responses, resulting in a 39.5% response rate (95% CI, 29.2–49.9). The difference observed between treatment groups was not statistically different or clinically relevant.

Overall survival

All patients on the DZ arm qualified for the analysis of overall survival; 36 patients died in the DZ arm, resulting in a censoring rate of 56.6%. All patients on the DP arm qualified for the analysis of overall survival; 38 patients died in this arm, resulting in a censoring rate of 55.8%. The median survival time was 27.8 months (95% CI, 14.8–34.3) in the DZ group and 22.2 months (95% CI, 19.5–39.4) months in the DP arm. Because of the high censoring rate (approximately 55%), no difference between the treatment groups could be detected ($P = 0.99$).

For both duration of response and time-to-treatment failure, the difference between treatment groups was neither statistically significant nor clinically relevant.

Table 1 Summary of all grade 3 and 4 laboratory toxicity

Laboratory toxicity	Number (%) patients			
	DZ ($N = 83$)		DP ($N = 86$)	
	Grade 3	Grade 4	Grade 3	Grade 4
Anaemia	–	–	1 (1.2)	–
Hyperglycaemia	1 (1.2)	–	1 (1.2)	–
Hypokalaemia	1 (1.2)	–	1 (1.2)	1 (1.2)
Hyponatraemia	–	1 (1.2)	1 (1.2)	–
Increased ALT	–	1 (1.2)	–	–
Increased AST	–	1 (1.2)	–	–
Increased GGT	1 (1.2)	–	–	–
Leukopaenia	11 (13.3)	9 (10.8)	10 (11.6)	6 (7.0)
Lymphopaenia	1 (1.2)	3 (3.6)	–	1 (1.2)
Neutropaenia	4 (4.8)	45 (54.2)	6 (7.0)	43 (50.0)
Thrombocytopaenia	1 (1.2)	1 (1.2)	–	–

ALT alanine amino transferase, *AST* aspartate aminotransferase, *DP* docetaxel plus placebo, *DZ* docetaxel plus zosuquidar.3HCl, *GGT* gamma glutamyl transferase, *N* number of patients

Safety

On the DZ arm, one patient was randomly assigned to treatment but never received study drugs. A total of 42 of the 83 drug-treated patients (50.6%) completed six cycles of therapy, the maximum number of cycles allowed without additional consultations with the Lilly clinical research physician and investigator. The median number of cycles administered to drug-treated patients was 6.0 (range, 1.0–14.0 cycles). On the DP arm, 45 of the 86 drug-treated patients (52.3%) completed 6 cycles of therapy. The median number of cycles was 6.0 (range, 1.0–20.0 cycles).

The grade 3 and 4 laboratory toxicities are summarized in Table 1.

A total of seven patients died during the course of this study. On the DZ arm, three patients died; the deaths were due to cardiac failure, septic shock, and an unknown cause. The investigator determined that the cardiac failure and septic shock were possibly study drug-related. On the DP arm, four patients died: two from study disease, one from sepsis, and one from meningitis. In the investigator's opinion, the event of sepsis was possibly study drug related.

A total of 62 patients experienced serious adverse events (SAEs): 35 of the 83 patients (42.2%) on the DZ arm and 27 of the 86 patients (31.4%) on the DP arm. Of those patients, 54 had SAEs that were possibly study drug-related: 33 of the 83 patients (39.8%) on the DZ arm and 21 of the 86 patients (24.4%) on the DP arm. Twelve patients had serious, unexpected, and reportable adverse events: 6 of the 83 patients (7.2%) on the DZ arm and 6 of the 86 patients (7.0%) on the DP arm. One hundred sixty-eight patients experienced treatment-emergent adverse events: 82

of the 83 patients (99.0%) on the DZ arm and all patients on the DP arm. Seventeen patients discontinued due to adverse events: 7 of the 83 patients (8.4%) on the DZ arm and 10 of the 86 patients (11.6%) on the DP arm. Adverse events possibly related to study drugs that caused patients on the DZ arm to discontinue were: dizziness, fatigue, febrile neutropaenia, hypersensitivity, paraesthesia, peripheral edema, and peripheral neuropathy. Adverse events possibly related to study drugs that caused patients on the DP arm to discontinue were: anaphylactic reaction, edema, febrile neutropaenia, hypersensitivity, peripheral neuropathy, peripheral sensory neuropathy, and skin desquamation. Among adverse events on either treatment arm, no apparent trends were evident.

Discussion

An interpretation of the impact a P-gp inhibitor has on efficacy results must be balanced with a thorough understanding of the safety results. Improvement in efficacy can result from pharmacokinetic interactions that increase exposure to the chemotherapy. In this case, increased toxicity would also be expected. This has been true with many P-gp inhibitors administered previously. Because of this, the dose of the chemotherapeutic agent was reduced in the investigative arm. To evaluate whether the addition of a P-gp inhibitor to the standard docetaxel regimen derives a beneficial pharmacodynamic effect, a randomized study in which the coadministered chemotherapy was given at the full dose, was required. This study represents one of the few studies in which such a comparison has been possible and is the only such study in breast cancer.

Regarding efficacy, the evaluation of time to progressive disease shows there to be a statistically significant, although clinically insignificant, difference between the two arms in favor of the placebo group. This is a surprising result and may indicate that there is either no effect of P-gp inhibition or that the treatment reduces the prognosis as measured by this outcome. The difference in efficacy may be explained by the difference in docetaxel dose intensity as a consequence of increased toxicity due to the addition of zosuquidar.3HCl. However, the docetaxel dose intensity in this study was equivalent between arms (DZ = 90.7% and DP = 92.5%); therefore, it is not likely to be the reason for the difference in efficacy. Alternatively, the arms may not have been balanced between treatment groups with respect to a key prognostic variable: duration of response to prior adjuvant or neoadjuvant therapy. Patients were stratified according to exposure to prior anthracyclines and whether they had relapsed within 6 months following the initiation of neoadjuvant or adjuvant chemotherapy. Prior anthracycline exposure had no bearing on outcome. However, while the numbers of patients in each strata based on time to relapse following initiation of neoadjuvant or adjuvant therapy were balanced between treatment groups, the actual duration of the response to adjuvant or neoadjuvant therapy was different between the two arms (34.7 months on DP vs. 25.4 months on DZ).

When this variable was controlled, the difference in progression-free survival was no longer significant. Extending this analysis to investigate the effect of zosuquidar.3HCl on patients relapsing within 12 months following their neoadjuvant or adjuvant chemotherapy, the relative risk or relapse was 1.75 for the DZ arm and 3 for the DP arm, indicating a possible beneficial effect on these patients.

With respect to the other efficacy parameters there was no difference in response rate or the median duration of response, and there was also no difference in time-to-treatment failure or overall survival. However, in the analysis of time-to-treatment failure and overall survival, the censoring rates were excessively high (>55%), precluding meaningful analysis. In the evaluation of safety there was no difference in the number of deaths or discontinuations between the groups. Additionally, no apparent difference existed in the frequency of most laboratory and nonlaboratory toxicities. More detailed analyses of hematologic parameters indicated that the DZ arm had statistically significant reductions in total white blood cells and platelets when compared to the control, DP. Although statistically significant, the difference in platelet count was not of clinical concern. No difference was found for neutrophils or lymphocytes. There was a statistically significant difference in the occurrence of febrile neutropaenia (relative risk on DZ compared to on DP = 1.83) that may indicate a difference in some aspects of the hematologic toxicity between the arms resulting from P-gp inhibition in CD34+ cells.

A complete evaluation of the efficacy, and in particular the safety data, can only be performed together with an analysis of the pharmacokinetic (PK) data. While PK data are not included in this report, it does, however, appear that zosuquidar.3HCl 500 mg administered twice daily for 1 day can be safely administered with a full dose of docetaxel (100 mg/m^2) without excess toxicity. Given the toxicity of single-agent docetaxel, particularly in the presence of liver compromise, this is a significant advance in the modulation of MDR.

Although the results of this study demonstrated a limited use of zosuquidar.3HCl when administered with docetaxel in the treatment of women with metastatic or locally recurrent breast cancer, its use is being explored in treatment of various haematological malignancies. Zosuquidar.3HCl was administered intravenously with daunorubicin and cytosine arabinose to 16 patients with acute myeloid leukaemia in a phase I dose-ranging clinical trial. Eleven patients achieved a complete remission and one a partial

remission with a median survival of 559 (range, 38–906) days. Non-haematological grade 3 and 4 toxicities were seen in 4 patients. Zosuquidar.3HCl infusion was associated with rapid inhibition of Rh123 efflux in CD56+ cells in 16/16 patients and in CD33+ cells in 6/10 patients. The median inhibition was 95% for C56+ cells and 85.25% for CD33+ cells. The median IC50, using a MTT assay for daunorubicin, decreased significantly between zosuquidar.3HCl modulated and unmodulated cells ($n = 11.153$ and 247 ng/mL, respectively, $P = 0.01$) [12].

A further small phase I/II trial was performed whereby zosuquidar.3HCl was given orally in combination with the CHOP regimen to 15 patients with non-Hodgkin's lymphoma. At doses of 500 mg of zosuquidar.3HCl, there was minimal toxicity and no observed enhancement of CHOP-related toxicity. In addition, zosuquidar.3HCl did not significantly affect the pharmacokinetics of doxorubicin and had moderate effects on the pharmacokinetics of vincristine [13].

Conclusions

The combination of zosuquidar.3HCl plus docetaxel at the doses used in this study is safe. Although a significant increase in the relative risk of neutropenic fever was found, there was no evidence to suggest that the inclusion of zosuquidar.3HCl compromised treatment because there was no statistically significant difference between arms in the intensity of docetaxel or in the numbers of deaths or discontinuations. The analysis of efficacy data is complex, but it can be concluded that there is no difference in progression-free survival, overall survival, or response rate in the study as a whole. Prior anthracycline treatment did not appear to effect outcome, but time to relapse from neoadjuvant or adjuvant treatment did have an effect on progression-free survival.

Exploratory analyses incorporating this information highlighted a possible beneficial use for zosuquidar.3HCL in patients who have relapsed in less than 12 months from their previous treatment. A larger sample size study comparing single-agent docetaxel to docetaxel plus zosuquidar.3HCl at the doses administered in this study in this population should perhaps be undertaken to further explore this novel hypothesis.

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Conflict of interest statement None.

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