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CLINICAL TRIAL REPORT

TEXAS (Taxotere® EXperience with Anthracyclines Study) trial: mature results of activity/toxicity of docetaxel given with anthracyclines in a community setting, as first line therapy for MBC

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Abstract
Purpose The TEXAS (Taxotere® EXperience with Anthracyclines Study) study examined docetaxel in combination with an anthracycline, as first line treatment of metastatic breast cancer (MBC), in everyday practice, and compared the findings with a randomised controlled trial.
Methods Four hundred and seventy patients were registered on the TEXAS trial. Patients were assigned, according to treating clinician's discretion, to either doxorubicin 50 mg/m^2 or epirubicin 75 mg/m^2 both given day1 15 min intravenous bolus every 3 weeks, followed by docetaxel 75 mg/m^2, day 1, 1 h intravenous infusion every 3 weeks.
Results The overall response rate (ORR) was approximately 61%. The main toxicity reported was neutropenia, with 75 patients (55%) in the AT group and 203 (61%) in the ET arm. Febrile neutropenia or neutropenic sepsis was reported for 32 (24%) of the AT arm and 78 (23%) of the ET arm.
Conclusions This open access study demonstrates that AT or ET are highly active treatments for MBC, with similar response rates to those observed in a phase III clinical trial. This may be important for patients with rapidly progressive visceral disease. Side effects can be managed effectively with growth factors and/or prophylactic antibiotic.

Keywords Chemotherapy · Metastatic breast cancer

Conflict of interest: An educational grant was provided from Aventis to organise the study. Taxotere was provided free of charge for patients in the study.

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Introduction

Taxanes and anthracyclines are two of the most active compounds used to treat breast cancer. Single agent doxorubicin has shown overall response rates of between 35 and 50% in patients with metastatic breast cancer (MBC) who have not previously received chemotherapy [1], and in a head to head trial of these single agents in patients being given first line therapy

for MBC, docetaxel was shown to have superior efficacy with a 48% response rate compared to 33% for doxorubicin [2]. Data have shown that there is a lack of cross-resistance between these two agents, which led to the development of trials of these drugs in combination [3]. Data from the Intergroup trial E1193, comparing doxorubicin versus paclitaxel versus doxorubicin and paclitaxel given together showed response rates of 36, 34 and 47%, respectively. However, overall survival was not significantly different between the three groups, no differences in changes in quality of life scores from baseline were found between any of the groups. . Patients receiving single agent doxorubicin and single agent paclitaxel crossed over to the other agent at progression [4].

Docetaxel, which has a different activity and toxicity in the 3-weekly schedule as compared to paclitaxel, has been combined with an anthracycline, and is an effective first-line treatment for patients with MBC. The phase III study (TAX 306) demonstrated that doxorubicin plus docetaxel (AT) is more effective than doxorubicin plus cyclophosphamide (AC) [5]. The combination of docetaxel and epirubicin has similarly been shown to be very effective, with what investigators considered to be acceptable tolerability in a trial setting [6].

TAX 306 [5] was an international, multicentre, randomised, non-blinded phase III study of 429 patients, comparing up to 8 cycles of doxorubicin (50 mg/m^2) and docetaxel (75 mg/m^2) (AT), given D1 q3w against doxorubicin (50 mg/m^2) and cyclophosphamide (600 mg/m^2) (AC), given D1 q3w. The main objective was to compare time to progression, with further comparisons of overall response rates, time to treatment failure, toxicity and quality of life.

Overall AT significantly improved time to progression and overall response rate, compared to AC. However, there was no difference in overall survival. The most common toxicities with both trial arms were haematological, the incidence of grade 3/4 neutropenia and febrile neutropenia were significantly greater in the AT arm.

Recent experience has shown the value of confirming the results obtained in a highly controlled clinical trial settings in a situation that more closely reflects real-life clinical practice [7, 8]. Therefore, we chose to examine the activity and tolerability of these two agents in combination in a less rigorously selected population of women attending UK oncology centres. TEXAS (Taxotere® EXperience with Anthracyclines Study) examined docetaxel in combination with an anthracycline, either doxorubicin or epirubicin, in everyday practice, and compares the findings with those observed in a phase III setting (the TAX 306 trial).

Patients and methods

Women with metastatic breast cancer were included in the study. The main inclusion criteria were, WHO performance status 0, 1, or 2; age 18 years or over; normal cardiac function, assessed according to local hospital policy; adequate haematological function (neutrophils $\geq 1.5 \times 10^9$/l, platelets $\geq 100 \times 10^9$/l, haemoglobin ≥ 10 g/dl); hepatic function (total bilirubin <1 UNL, AST and/or ALT ≤ 2.5 UNL, alkaline phosphatases ≤ 5 UNL) and renal function (creatinine < 175 μmol/l).

Prior adjuvant or neoadjuvant chemotherapy was allowed. However, if prior treatment contained an anthracycline or taxane, at least 12 months must have elapsed before study entry. The maximum allowable anthracycline dose prior to entry was doxorubicin 250 mg/m^2; epirubicin 300 mg/m^2; mitoxantrone 52 mg/m^2. There was no upper limit on previous taxanes. Prior hormonal or radiotherapy was allowed. Two hundred sixty four patients (56%) had received adjuvant or neoadjuvant chemotherapy, and 62 (13%) had received anthracyclines. None of the TEXAS patients had received prior taxanes.

Patients were excluded if they had received prior chemotherapy for metastatic disease; had brain metastases; were pregnant or lactating; had any unstable medical conditions or contra indications to docetaxel or anthracyclines; had definite contra indications for the use of corticosteroids, either through previous severe hypersensitivity reaction, or if their diabetes was unable to be managed if oral steroids were given. Patients were not able to take part in the study if they had concurrent treatment with other experimental drugs or any anti-cancer cytotoxic treatment or had participated in another trial with an investigational drug 30 days prior to study entry.

Study design

This was a multicentre, non-randomised, open-evaluation study examining docetaxel in combination with epirubicin or doxorubicin as first line chemotherapy for metastatic breast cancer.

Objectives

The primary objective was to assess whether the results obtained in the experimental arm (AT) of a controlled

phase III clinical trial of metastatic breast cancer were reproducible in this study undertaken in the UK clinical setting in terms of overall response rate, time to progression and survival. The secondary objective was to assess the efficacy and tolerability of a docetaxel–anthracycline combination as first-line chemotherapy for patients with MBC in the 'real life' community setting.

Study population and patient characteristics

Between November 1999 and October 2001, 470 patients were registered on the TEXAS trial. No data were available on treatment and outcomes for 1 patient, 136 patients were assigned to the doxorubicin and docetaxel (AT) group, and 333 were assigned to the epirubicin and docetaxel (ET) group, these patients comprised the ITT population. Patient baseline characteristics are shown in Table 1. For those patients who had been diagnosed with early breast cancer (388, 83%) the median time from first diagnosis to start of TEXAS therapy was 3 years and 8 months.

Treatment

Patients were assigned, according to the treating clinician's discretion, to either doxorubicin 50 mg/m^2, day 1, 15-min intravenous bolus every 3 weeks or epirubicin 75 mg/m^2, day 1, 15-min intravenous bolus every 3 weeks, followed by docetaxel 75 mg/m^2, day 1, 1-h intravenous infusion every 3 weeks. The use of these doses of anthracycline was standard at the time and were based on what was then considered to be equivalence. Dexamethasone 8 mg bd p.o., was given as prophylactic premedication to inhibit fluid retention the day before the infusion, the day of the infusion and the day after the infusion. This was given in over 98% of cases. The routine use of prophylactic ciprofloxacin was recommended at 500 mg p.o. twice a day for 10 days starting on day five. Ciprofloxacin was given in 84% of cycles, 91% in the AT group and 82% in the ET group.

The protocol stated that the lifetime cumulative dose of 550 mg/m^2 of doxorubicin or 900 mg/m^2 of epirubicin should not be exceeded at any time. If the cumulative dose of 550 or 900 mg/m^2 was reached the treatment with the anthracycline was stopped but the clinician was able to continue treatment using docetaxel single agent (100 mg/m^2) for as long as they considered it appropriate.

Table 1 Baseline patient characteristics

Patient characteristics	Docetaxel and doxorubicin	Docetaxel and epirubicin
No. of patients	136	333
Median age, years (range)	48 (25–70)	50 (26–69)
WHO performance status		
0	50 (37%)	173(52%)
1	72(53%)	133(40%)
2	14 (10%)	27 (8%)
HER2 Status		
+ve	4 (3%)	18 (5%)
–ve	15 (11%)	39(12%)
Not known	117 (86%)	276(83%)
Previous chemotherapy	60 (44%)	203 (61%)
Radiotherapy	91 (67%)	232 (70%)

Assessments

Adverse events and toxicities were assessed after every cycle. Safety analyses were carried out on the intention to treat (ITT) population. Toxicity was graded according to the NCI common toxicity criteria.

Tumour response was assessed during treatment according to UICC criteria as judged by the treating clinician. No central audit of treatment response was undertaken as this was in keeping with real-life clinical practice

Results

The median number of cycles received was 6, with a median cumulative dose of 420 mg/m^2 of docetaxel and a median cumulative dose of 300 and 450 mg/m^2 for doxorubicin and epirubicin, respectively. Overall 323 patients (69%) received at least 6 cycles, 89 (65%) received at least 6 cycles of AT and 234 (70%) received at least 6 cycles of ET. Prophylactic growth factors were given in 441 (17.8%) cycles. One hundred and fifty two patients discontinued treatment, although not all prior to receiving cycle 6. Reasons for treatment discontinuation included disease progression (67, 14%; ET 46, 14%; AT 21, 15%), adverse events (63, 13%; ET 38, 11%; AT 22, 16%) and withdrawal of consent (11, 2%; ET 10, 3%; AT 1, 1%).

Efficacy

Data on tumor response were available for 108 (79%) of the AT group and for 293 (87%) of the ET group. Tumor response (ITT) is shown in Fig. 1. The overall response rate (ORR), where known, was 61% (n = 66) for patients treated with docetaxel and doxorubicin, and 62% (n = 182) for patients treated with docetaxel and epirubicin. There was no significant difference in response between the two groups (P = 0.71).

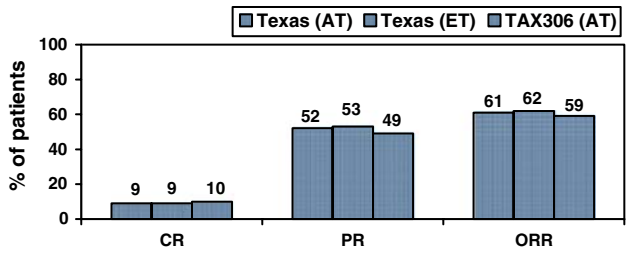

Fig. 1 Response to treatment (ITT)

Survival

Data on time to progression and survival were analysed at a median follow up of 72 weeks, at this time 433 (92%) had progressed following first line therapy and 401 (85.5%) had died.

Progression-free survival

Overall median time to progression was 9 months, (9 months for ET and 8 months for AT). See Table 2.

Overall survival

Overall median survival was 17 months, this was slightly more for patients who were given ET, 18 months (95%CI 15,20) compared to 15 months (95%CI 12,17) for those given AT, see Table 3. Three hundred and three patients [65% survived for over 1 year, 173 (37%) for over 2 years and 99 (21%) for over 3 years].

Safety

Safety analyses were performed in the ITT population. Toxicities were graded according to NCI criteria and were recorded in the case record forms every two cycles. The main toxicity reported was neutropenia, with 75 patients (55%) in the AT group and 203 (61%) in the ET arm with NCI grade 3 or 4 neutropenia. Febrile neutropenia or neutropenic sepsis was reported for 32 (24%) of the AT arm and 78 (23%) of the ET arm. There were 3 (0.9%) deaths from neutropenic sepsis in the ET arm and 2 (1.5%) in the AT arm.

The most common non-haematologic toxicities were diarrhoea, nausea, vomiting, and pyrexia. These data are shown in Table 4.

Thirty-eight (11%) of patients treated with ET and 22 (16%) treated with AT withdrew from the treatment due to an adverse event. Two patients received minimal amounts of docetaxel (<12 mg/m^2 in total), as the infusion was stopped due to an allergic reaction and they were not rechallenged, a further five were withdrawn after cycle 2 due to suspected allergic reaction to docetaxel. One patient in the ET arm had congestive heart failure after 6 cycles of treatment and 3 patients were withdrawn after cycle 1 or 2 due to cardiac dysrhythmia.

Table 3 Overall survival

Time to death in months	TEXAS overall	Docetaxel and doxorubicin	Docetaxel and epirubicin
N	469	136	333
Deaths	401	117	284
Median	17	15	18
lcl	15	12	15
ucl	18	17	20

Discussion

In this community-based, open evaluation study, docetaxel, in combination with either doxorubicin or epirubicin, was shown to be highly effective, achieving ORRs of 61 and 62%, respectively. These figures confirm those achieved in the docetaxel–doxorubicin arm of the phase III TAX 306 trial (ORR 59%). Both groups in the TAX 306 trial and both groups in the TEXAS study compared favourably in terms of response rates and TTP with single-agent chemotherapy in phase III trials [4, 9, 10].

Table 2 Time to progression

Time to progression/ death in months[a]	TEXAS overall	Docetaxel and doxorubicin	Docetaxel and epirubicin
N evaluable	433	120	313
Events	416	116	300
Median	9	8	9
lcl	8	7	8
ucl	9	9	10

[a]If a patient died without progression being recorded, date of progression was taken as date of death

Table 4 Grade III/IV non-haematologic toxicity (ITT)

	Docetaxel and doxorubicin	Docetaxel and epirubicin	TAX 306 (AT arm)
Alopecia[a]	69 (51%)	183 (55%)	202 (95%)
Diarrhoea	6 (4%)	17 (5%)	16 (8%)
Nausea	7 (5%)	15 (4%)	12 (6%)
Vomiting	9 (7%)	13 (4%)	12 (6%)
Pyrexia	4 (3%)	18 (5%)	Not reported
Fatigue	10 (7%)	9 (3%)	Not reported

[a]Alopecia grade 1 and 2 only

In the TAX306 study [5] there was no significant difference in overall survival at a median follow up of 49 months, with median survival of 22.5 months in the AT group versus 21.7 months in the AC group. However, approximately 60% of patients in each treatment group received additional chemotherapy, including 40% in the AC group and 12% in the AT group who received a taxane. Overall 29% of patients in the AC group and 6% of patients in the AT group had further chemotherapy with docetaxel. Thus there was a high rate of cross-over to docetaxel in the AC group. Texas data on survival show a median survival of just under 17 months. This is less than the TAX306 study, however the median follow up for TEXAS was 17 months compared to 49 months in the TAX306 study, longer follow up data will be needed to see whether overall survival in this community-based study was similar to the original trial. The proportion of patients surviving 1, 2 and 3 years was also slightly higher in the TAX306 study (78 vs. 65% 1 year; 46 vs. 37% 2 year and 28 vs. 21% 3 year survival). This may be because performance status in TAX306 was higher at baseline than the TEXAS study, median Karnofsky performance status of 90%—equivalent to WHO PS of 0—whereas the median WHO performance status for TEXAS was 1.

In the TAX306 study the main toxicity in both arms was myelosuppression, 97% AT and 88% AC. There was significantly more febrile neutropenia in patients receiving AT (33 vs. 10% AC), although no deaths from neutropenic sepsis were reported. Neutropenia was also the main toxicity for patients in the TEXAS study, with over 55% experiencing grade 3 or 4 neutropenia and over 23% febrile neutropenia or neutropenic sepsis. Lower levels of neutropenia in the TEXAS trial may have been due to less stringent requirements for SAE reporting. However, reported levels of febrile neutropenia and neutropenic sepsis were similar.

Severe non-haematological toxicities were uncommon in both AT and ET groups of TEXAS. Despite a median cumulative dose of docetaxel of 420 mg/m^2, severe docetaxel-specific toxicities (such as oedema and nail changes) were rare. This reflected incidence of non-haematologic toxicities recorded in TAX306.

TEXAS data on cardiac toxicity also showed relatively low levels of cardiac toxicity. In TAX306 four percent of patients receiving AT stopped treatment due to cardiac problems, compared with 8% on AC. Rates of CHF (AT 3% and AC 4%) were similar to those experienced with anthracyclines given as a single agent [11, 12]. These data confirm data from other studies, which show that there is unlikely to be a pharmacokinetic relationship between docetaxel and anthracyclines [13, 14].

Lower levels of myelotoxicity have been seen in trials combining paclitaxel with an anthracycline. A number of phase III trials have used anthracyclines with paclitaxel as first line therapy for MBC [15–18]. However, the results from these studies have been inconsistent and have shown contradictory benefits for this combination compared to the non-taxane standard arm, as well as generally lower activity, when compared indirectly with the docetaxel/anthracycline results presented here and in the TAX 306 trial.

Data on single agent docetaxel showed useful objective response rates of 47% in women who had received prior alkylating chemotherapy (43% received in the advanced setting) with relatively low levels of febrile neutropenia (5.7%) or neutropenic infection (2.5%) [2]. Another study of single agent docetaxel recorded an ORR of 30% in women who had failed anthracycline treatment, either in the adjuvant or first line metastatic setting [8]. More recently, although inferior to docetaxel in respect of response rate and time to progression in a 3 weekly schedule [19], single agent weekly paclitaxel has shown good efficacy, with an ORR of 40% compared to 28% for 3 weekly paclitaxel, with lower reported levels of grade 3 neutropenia (8 vs. 15%, respectively) [20]. The data suggest that 3 weekly single agent paclitaxel is less active in treating first line metastatic breast cancer than weekly paclitaxel. A randomised controlled trial of weekly versus 3 weekly paclitaxel (Will Weekly Win) is due to finish recruitment in the UK shortly and should provide a definitive answer to this question. Combination paclitaxel and gemcitabine, given 3 weekly has shown an ORR of 39.3 versus 26% for single agent paclitaxel [21]. Again rates of neutropenia were higher for the combination treatment 17.2%, compared to single agent 6.6%. Taxotere given with capecitabine has also shown superiority compared with the single agent taxane in a phase III trials of women pretreated with anthracyclines, ORR 42 versus 30% [22]. In this study, however, the combination therapy had lower reported levels of neutropenic fever, arthralgia and pyrexia but increased gastrointestinal adverse events and hand–foot syndrome. There are seemingly, therefore advantages and disadvantages to the various single agent and combination taxane programmes.

Conclusions

This open access study demonstrates that AT or ET are highly active treatments for metastatic breast cancer. This may be important for patients with rapidly progressive visceral disease. Provided that it is

recognised, side effects can be managed effectively with growth factors and/or prophylactic antibiotic. Otherwise given its manageable short-term side-effect profile and lack of significant long-term toxicity, the anthracycline/docetaxel combination remains an option for first-line therapy for MBC.

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