Report

Phase III randomized trial of droloxifene and tamoxifen as first-line endocrine treatment of ER/PgR-positive advanced breast cancer

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Summary

Purpose: This trial was designed to demonstrate equivalence between droloxifene 40 mg/d and tamoxifen 20 mg/d as first-line treatment in pre- and post-menopausal women with ER+ and/or PgR+ advanced breast cancer based on time to disease progression and tumor response.

Materials and methods: One thousand three hundred fifty four women with measurable disease, previously untreated by hormonal or chemotherapy for advanced or recurrent breast cancer, were enrolled by 179 institutions in 35 countries. Patients were stratified at baseline for menopausal status. Patients receiving adjuvant hormonal therapy within 1 year were excluded. All patients gave written informed consent, were randomized to 40 mg droloxifene or 20 mg tamoxifen daily as single-agent therapy and underwent tumor assessment every 3 months. A central committee reviewed digitized images for all cases of tumor progression or objective response.

Results: The hazard ratio (droloxifene/tamoxifen) for the primary endpoint, time to disease progression, was 1.287 favoring tamoxifen (95% C.I.: 1.114–1.487; $p < .001$). The objective response rate (CR + PR) was 22.4% for droloxifene and 28.6% for tamoxifen ($p = .02$). Tamoxifen was superior to droloxifene overall, among both pre- and postmenopausal patients and among patients ≤65 years; there was no difference among women >65 years. The hazard ratio for all-cause mortality was 0.871 (95% C.I.: 0.672–1.129; $p = .29$), favoring droloxifene but not statistically significant.

Conclusions: Droloxifene was significantly less effective than tamoxifen overall and particularly among women under 65 years. Tamoxifen and droloxifene were both less effective in pre-menopausal women with receptor-positive disease compared to post-menopausal women. Further clinical development of droloxifene was stopped.

Introduction

Droloxifene is a novel selective estrogen receptor modulator (SERM) whose potential as a treatment for breast cancer has been suggested by several non-comparative studies [1–8]. Preclinical studies [9, 10] have shown that droloxifene has a shorter serum half-life and a higher affinity for the estrogen receptor than tamoxifen, an accepted first-line treatment option for many women with hormonally sensitive breast cancer.

*For the Droloxifene 301 Study Group.

Pre-clinically, the two agents differ most with respect to animal carcinogenicity, with tamoxifen shown to cause hepatic tumors in 98% of treated animals while droloxifene- and control-treated animals showed a 1–2% incidence [10]. In humans, of course, it is well known that tamoxifen increases the incidence of endometrial cancer but has no effect on the incidence of hepatic tumors. Nevertheless, these pre-clinical findings suggested that droloxifene might be more useful than tamoxifen for longer-term breast cancer therapy, such as in the adjuvant setting, provided that droloxifene possessed efficacy that was at least equivalent to tamoxifen in patients with advanced disease. A Phase 2 study of 369 women with advanced breast cancer randomized to one of three doses of droloxifene (20, 40 or 100 mg/d) as first-line hormonal therapy gave encouraging results, with CR + PR rates of 30, 47 and 44%, respectively, for the three treatment groups [6]. Droloxifene has also been studied in patients with advanced breast cancer who have been exposed to prior endocrine treatment, including some who were resistant to tamoxifen, with partial response seen in 15% of these patients [11]. The purpose of the present study was to demonstrate equivalence between droloxifene 40 mg daily and tamoxifen 20 mg daily by comparing time to disease progression in a global study intended to reflect the diversity of the patient population actually using first-line hormonal therapy for advanced breast cancer.

Materials and methods

Study design

This was a prospective, randomized, active-control, double-blind, multi-center, parallel-group comparison of droloxifene and tamoxifen, in women with ER+ and/or PgR+ advanced breast cancer. Patients were stratified by menopausal status. The primary endpoint of the trial was time to disease progression, defined as the time from randomization to the first objective finding demonstrating a 25% increase in the size of at least one tumor lesion or the appearance of any new tumor lesion or death due to breast cancer. Overall tumor response was a secondary endpoint, along with response duration and various subset analyses. Time to progression and tumor response were determined for every patient by a central endpoint evaluation committee. Parameters used to pre-define subsets of patients in the prospective statistical analysis plan included age, menopausal status, geography, disease status at baseline, adjuvant therapy, and performance status as listed in Table 4. The independent Data Safety Monitoring Board (DSMB) conducted periodic, planned interim analyses of the data in order to monitor the safety of the trial.

Patient selection

Eligible patients included pre- or post-menopausal women with biopsy-proven breast cancer with distant metastases, locoregional recurrences not suitable for local therapy or inoperable primary tumors. Patients were defined as postmenopausal if menses had ceased for more than 1 year and serum estrogen was below 30 pg/ml, or if the patient had undergone bilateral oophorectomy. Acceptable target lesions were measurable in at least one dimension, at least 1 cm in size and not previously radiated. Lytic bone lesions not visible on plain x-ray were excluded as target lesions, as were any blastic bone lesions or blastic portions of mixed lesions. Patients were excluded if they had received any prior chemo- or hormonal therapy (including oophorectomy) for advanced disease, or adjuvant hormonal therapy within the past year or adjuvant chemotherapy within the past month prior to randomization. Patients were required to have receptor-positive tumors defined as ER+ and/or PgR+ (unknown receptor status for both ER and PgR was not allowed). ECOG performance status of 60% or greater was required. Patients with brain, leptomeningeal or extensive (>1/3 of the liver) hepatic metastases were excluded, as were patients with hypercalcemia or significant risk for thromboembolic events.

Pretreatment evaluation

Prior to initiating study drug treatment, a complete history, physical exam and tumor assessment were performed, including bone scan, chest x-ray, and abdominal CT (or liver ultrasonography). Any suspicion of bone metastases on the bone scan required a defined set of eight skeletal plain films for confirmation. Representative tumor lesions were identified for each patient. Tumor response or progression would be determined based upon changes in these target lesions. Any new lesion was deemed disease progression regardless of changes in target lesions.

Treatment plan

Each patient received, by random assignment, either (a) 40 mg/day droloxifene (Pfizer Central Research,

Groton, CT) + placebo tamoxifen or (b) 20 mg/day tamoxifen (Tamoxpuren®, Klinge Pharma, Munich, Germany) + placebo droloxifene.

Follow-up tumor assessments

After randomization, patients returned to clinic every 3 months. At each visit, physical examination, chemistry/hematology, chest x-ray, and measurement of target lesions were performed for all patients. Abdominal CT (or hepatic sonography) and/or bone scan with skeletal x-ray series were performed every 3 months for those patients with relevant target lesions at baseline. Patients with no target lesions in either bone or liver received abdominal CT and bone scan at 6 month intervals and at the end of the study.

Response evaluation

Target lesion measurements were recorded in a log every 3 months. All physical examination measurements were checked for errors between the medical record and the case report forms by monitors who visited each study center at least every 4–8 weeks. All x-ray and scan images of target lesions, or new lesions, were first evaluated by each investigator in order to determine the clinical plan for the patient. These films were then sent to a central imaging facility where each x-ray or scan was digitized for electronic review by an Endpoint Classification Committee (ECC) consisting of experienced investigators and radiologists from North America and Western Europe. Electronic images were viewed on a bank of four ultra-high resolution monitors using software that allowed contrast adjustment to optimize image readability of x-rays and scans. The reviewers were blinded to treatment arm. Tumor response was evaluated according to WHO criteria [12], with additional requirements that (i) only x-ray, CT or MRI (not radionuclide bone scan) were used to determine response or progression in bone, and (ii) blastic bone lesions, or the blastic portion of mixed lytic/blastic bone lesions, were not considered for tumor response evaluation. The decision of the committee regarding objective tumor response and the date(s) related to that response was final as concerned the study analyses. This committee reviewed every case in which the investigator found CR, PR or disease progression, a death or a premature termination. At the close of the trial, all patients still receiving their assigned study medication underwent a termination visit and complete tumor assessment. Only those active patients whose disease status was unchanged at the time the trial closed, according to the investigator's review of the case, were accepted as 'no change' in the trial database without committee review.

Ethics

The ethical committee at each participating institution reviewed and approved the protocol and the informed consent document. Each patient gave written informed consent that met the requirements of FDA GCP regulations and the Declaration of Helsinki (as amended 1975 and 1983), in addition to all local regulations in each country as required.

Statistical methodology

The statistical plan predicted that the study would need to enroll 1375 patients in order to observe 900 events (disease progressions) within 2 years. Patients were assigned to study treatment by a computer-generated randomization list after stratification by menopausal status. The study was designed as a non-inferiority trial employing the technique of repeated confidence intervals [22]. The trial was planned to continue until 900 events had occurred in order to allow a determination that the relative efficacy of droloxifene was at least 80% that of tamoxifen as measured by the hazard ratio for time to disease progression. The operating characteristics of the statistical inference were such that the power was 90% to declare the non-inferiority of droloxifene relative to tamoxifen if the true times to disease progression for the two drugs were not different and approximately 900 events had been observed. The statistical plan allowed stopping the trial before 900 events for a statistically significant difference in efficacy, but required observation of 900 events in order to declare non-inferiority. Interim analyses were scheduled to occur with every 150 additional events and these results were provided only to the independent DSMB in order for them to review the progress and safety of the trial. However, the identity of each treatment arm remained coded until after the DSMB had made the decision to end the trial. The project medical and administrative staff, along with investigators and other study personnel, were unaware of any interim results.

Hazard ratios are estimated from univariate proportional hazards regression (Cox) models with treatment as the sole predictor. Lifetime analyses are based on the product-limit method of Kaplan and Meier. Confidence intervals and p-values reported herein are nominal, that is, unadjusted for multiple comparisons

Table 1. Geographic regions (randomized patients)

Africa/Mid-East (201 patients)	Egypt	South Africa	Israel
Asia (337 patients)	P. R. China India	Hong Kong	Taiwan
Eastern Europe (210 patients)	Russia Hungary Czech Republic	Serbia Latvia Slovakia	Belarus Poland
Latin America (91 patients)	Mexico Brazil	Argentina Chile	Costa Rica Uruguay
North America (252 patients)	Canada	United States	Puerto Rico
Western Europe (263 patients)	France Germany Netherlands Austria	United Kingdom Turkey Greece Spain	Sweden Belgium Norway Italy

or interim analyses. The log-rank test was used for comparisons of time to event distributions. The chi-square test was used for comparisons of response rates. All of the subgroup analyses shown in Tables 4 and 5 were included in the prospective statistical analysis plan and were hypothesis-testing analyses.

Results

Patient characteristics

A total of 1966 women with advanced breast cancer were screened for the trial and 1354 women were randomized between June, 1995 and December, 1997 at 179 study centers in 35 countries and territories (Table 1).

The pretreatment characteristics of the patients are shown in Table 2 according to treatment group. The two treatment groups showed no significant differences with respect to the parameters in Table 2, with the exceptions that the patients in the droloxifene group were somewhat more likely ($p < .05$; chi-square) to have four or more tumor lesions at baseline and to have received prior adjuvant hormonal or radiation therapy.

The mean duration of therapy was 196 days (range: 8–920 days) in the droloxifene group and 218 days in the tamoxifen group (range: 6–969 days). A total of 69 patients discontinued the study before disease progression occurred. Reasons for early termination are shown in Table 3. Under intention-to-treat principles, all randomized patients were included in the analyses of safety and efficacy.

Central review of endpoints

The ECC (ECC; A. Buzdar, Chairman) centrally reviewed 1026 patients for tumor response out of 1354 enrolled patients. A total of 328/1354 cases were reported by the investigator to be 'no change' at the time of the study data cut-off (February 1998); these cases were not submitted for review by the ECC. Every case involving disease progression or complete or partial response (CR or PR), as judged by the investigator, was reviewed centrally. The committee determined the nature of the response and the date of response or progression for the purposes of the analysis. The ECC was unable to adjudicate 36/1026 cases (3.5%) due to insufficient data.

Disease progression

Time to disease progression was the primary endpoint of the study. Figure 1 shows the time-course of disease progression for all randomized patients by treatment group. More than half of the patients (744/1354) experienced disease progression during the

Table 2. Pretreatment characteristics of randomized patients by treatment group and region (no. patients unless otherwise indicated)

		Droloxifene	Tamoxifen	Europe West	Europe East	Africa/M.E.	Asia	Latin America	North America
No. of patients randomized		681	673	263	210	201	337	91	252
Age	Under 45 years	115	96	7%	4%	14%	32%	13%	14%
	45–64 years	347	330	34%	56%	53%	57%	60%	42%
	65+ years	219	247	59%	40%	33%	11%	27%	44%
Menopausal status	Premenopausal	138	123						
	Postmenopausal	542	550						
Mean weight	(kilograms)	66.0	65.2						
Karnofsky score	80–100%	577	573	89%	87%	95%	80%	85%	77%
	60–70%	103	99	11%	13%	5%	19%	15%	23%
	<60%	1	1	0%	0%	0%	1%	0%	0%
Race	White	433	425						
	Asian	175	173						
	Black	26	25						
	Other	47	48						
	Not provided	0	2						
Disease at baseline	Recurrent disease, locoregional only	69	78	10%	6%	15%	11%	15%	11%
	Recurrent disease, distant metastases	297	270	48%	19%	24%	47%	38%	63%

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