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CLINICAL TRIAL

Phase II randomized clinical trial evaluating neoadjuvant chemotherapy regimens with weekly paclitaxel or eribulin followed by doxorubicin and cyclophosphamide in women with locally advanced HER2-negative breast cancer: NSABP Foundation Study FB-9

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Abstract Locally advanced breast cancer (LABC) is a good setting in which to monitor response to neoadjuvant chemotherapy, to downsize the tumor (which facilitates breast-conserving surgery), and to test newer agents in untreated patients. Eribulin (*E*) has shown activity in patients who have undergone previous taxane, anthracycline, and capecitabine treatment. We aimed to evaluate the neoadjuvant use of *E* followed by doxorubicin and cyclophosphamide (AC) in patients with HER2-negative LABC, using as a control a randomized group of women who received weekly paclitaxel (WP). Fifty women with LABC were accrued January–August 2013. Patients were randomized (1:2) to receive either WP ($N = 19$) for 12 treatments or *E* ($N = 31$) every 3 weeks for 4 cycles followed by AC every 3 weeks for 4 cycles before surgery. 17/19 patients who took WP and 25/30 who took *E* completed all cycles. Patients were evaluated by clinical examination and breast MRI at baseline and after completion of *E* or WP. Surgical pCR in breast and lymph nodes was determined by a local pathologist following chemotherapy. Forty-nine patients received ≥1 dose of neoadjuvant chemotherapy and are included in this analysis. Forty-eight underwent surgery; one had disease that was inoperable (on *E*) and is included as no-pCR patient. 17/19 of these patients who took WP completed 12 doses; 28/30 on *E* completed 4 cycles. Six discontinued treatment on WP, *E*, or AC. Both treatments were well tolerated. pCR on WP = 5/19(26 %) and on *E* = 5/30(17 %). Both regimens were equally well tolerated with no unexpected toxicities. pCR did not suggest higher activity with *E* than with other standard regimens in these LABC patients.

Keywords Breast cancer · Chemotherapy · Clinical trials · Neoadjuvant therapies

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Introduction

More than 234,000 women will be diagnosed with breast cancer in the US in 2015 [1]. A majority will be diagnosed with early stage breast cancer and treated with surgery

followed by adjuvant therapy based on final stage, biomarkers, and multi-gene assays to predict recurrence. However, approximately 30 % will present with stage IIB and III locally advanced breast cancer (LABC). For these patients with a more guarded prognosis, neoadjuvant chemotherapy is the accepted therapy for management of the disease. Its advantages include the ability to determine tumor response to a specific treatment regimen, increased potential for breast-conserving surgery, down-staging of axillary tumor involvement (which makes sentinel node sampling sufficient surgery for some patients), determination of prognosis-based pathologic complete response (pCR) as a surrogate endpoint for outcome, and the ability to procure preoperative tissue for the discovery of molecular and genetic correlates of response [2–6].

In several neoadjuvant phase II trials in locally advanced HER2-negative breast cancer, the NSABP Foundation evaluated the efficacy of newer agents to determine their potential benefit in an early disease setting. We examined nanoparticle albumin-bound paclitaxel followed by 5-fluorouracil/epirubicin/cyclophosphamide in patients with eligibility criteria similar to those in our current trial [7]. The overall pCR in breast and lymph nodes was 26 % (17 of 65), with 27 % (5 of 18) in triple-negative patients, and 11 % (3 of 28) in hormone-positive, HER2-negative patients. In a more recent study, the addition of pazopanib to weekly paclitaxel (WP) followed by doxorubicin and cyclophosphamide (AC) and post-operative pazopanib was tested in stage III, HER2-negative patients [8]. The overall pCR in breast and nodes was 17 % (16 of 93), with 9 % (6 of 67) in hormone-positive patients, and 38 % (10 of 26) in triple-negative patients. These studies are consistent with previously reported phase II neoadjuvant study pCR rates, which noted higher pCR in triple-negative patients than in those with non-triple-negative breast cancer [9, 10].

Eribulin mesylate (*E*) is a non-taxane that binds directly with tubulin, disrupting mitotic spindles, and inhibits microtubule polymerization. Because of its unique interaction with tubulin, this agent may have improved efficacy compared with existing microtubule-targeting therapies currently in use in the clinic [11–13]. Results from phase I studies established the preferred single-agent phase II dose of *E* as 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle. In a cohort of 33 patients on the 21-day schedule, only 18 % (6 of 33) of patients experienced dose interruptions, delays, reductions, or omissions during cycle 1, which decreased to only three patients in cycle 2. The most common drug-related grade 3–4 toxicities were as follows: neutropenia, 64 %; fatigue, 5 %; peripheral neuropathy, 5 %; and febrile neutropenia, 4 %. The objective response rate, all of which were partial responses (PR), was 11.5 % (95 % CI, 5.7–20.1), with a clinical benefit rate (defined as PR plus stable disease $\geq$6 months) of 17.2 % (95 % CI 10.0–26.8) [14–17].

A phase III study [18] compared *E* to the treatment of physicians' choice (TPC) in patients with locally recurrent or metastatic breast cancer who had undergone previous treatment with an anthracycline and taxane. There were 762 patients enrolled, including 508 treated with *E* and 254 with TPC. In the TPC arm, 96 % of patients received chemotherapy and 4 % were treated with a hormonal agent. The median number of prior chemotherapy regimens was four, and 73 % of patients had received capecitabine. The progression-free survival (PFS) favored *E*: 3.6 months versus TPC: 2.2 months (HR 0.76; 95 % CI 0.64–0.90, $p = 0.002$). Overall survival was increased to 2.47 months with *E* (HR 0.81; 95 % CI 0.66–0.99, $p = 0.041$) compared to TPC, with median survival of 13.12 and 10.65 months, respectively. The adverse event (AE) profile was similar to that previously reported in phase I/II studies [18–20].

On the basis of the survival advantage of *E* over TPC, the US FDA approved *E* as late-line therapy on November 15, 2010. Given the benefit in the advanced disease setting with an acceptable side effect profile, *E* appeared to be a good candidate to test both in earlier metastatic disease and in the neoadjuvant setting.

Patients and methods

NSABP FB-9 is a phase II, multi-center, randomized study of WP or *E* followed by AC as neoadjuvant therapy for women age $\geq$18 with HER2-negative LABC including stages IIB and IIIA–IIIC. Eligibility requirements included a diagnosis of invasive adenocarcinoma of the breast made by core needle biopsy or by limited incisional biopsy and a palpable mass in the breast or axilla measuring $\geq$2.0 cm by physical examination (PE); either hormone-receptor-positive or hormone-receptor-negative tumors; and HER2-negative status as assessed locally by immunohistochemistry or fluorescence in situ hybridization. Patients with inflammatory breast cancer were eligible without measurable disease.

Staging studies included a bone scan and liver imaging in patients with abnormal alkaline phosphatase or liver function tests, respectively. Patients were required to have an Eastern Cooperative Group (ECOG) performance status (PS) of 0–1, adequate bone marrow, hepatic and renal functions, and a baseline cardiac scan or echocardiogram within normal limits of the institution.

The primary aim of the study was to determine pCR in the breast and axillary lymph nodes following the completion of neoadjuvant therapy. The secondary aims of FB-9 included the determination of the pCR in axillary nodes, clinical complete response (cCR) rate, imaging response after WP or *E*, rate of breast-conserving surgery, and toxicity of the neoadjuvant regimens.

The Institutional Review Boards of each participating institution approved the study protocol, and all patients provided written informed consent. The study was conducted according to good clinical practice and the Declaration of Helsinki and its amendments.

Treatment

Patients in Arm 1 received WP 80 mg/m^2 for 12 doses followed by standard AC every 21 days for 4 cycles. Patients in Arm 2 received 4 cycles of *E* 1.4 mg/m^2 on days 1 and 8 of a 21-day cycle followed by standard AC, 60 and 600 mg/m^2, every 21 days for 4 cycles. Rules for dose modifications were similar for both agents. WP or *E* was withheld for any toxicity of grade $\geq$3 until improvement $\leq$grade 1. Grade 3 neuropathy required one dose-level decrease (WP from 80 to 70 mg/m^2 and *E* from 1.4 to 1.1 mg/m^2) and grade 4 required discontinuation of WP or *E*. Standard AC every 21 days was withheld for absolute neutrophil count (ANC) of grade 3. If a patient developed grade 3 or 4 neutropenia, granulocyte-colony-stimulating factor was permitted. Grade 3 non-hematologic toxicity required one dose-level reduction.

Surgery was planned after the patient completed chemotherapy and final tumor assessment was made. The choice of modified radical mastectomy or breast-conserving surgery was at the discretion of the surgeon and the patient. Axillary staging was required, but surgeons had the option to eliminate this if sentinel node biopsy following neoadjuvant therapy was negative or if sentinel node involvement was limited to one or two positive nodes with at least four negative sentinel nodes or non-sentinel nodes and a pCR in the breast. Radiotherapy of the breast was required for breast-conserving surgery, but decisions on post-mastectomy and regional nodal irradiation were left to the discretion of the investigator. Post-operative endocrine therapy for receptor-positive patients was required for a minimum of 5 years, with choice of agents determined by the investigator.

Response and safety assessment

Tumor measurement by physical examination and MRI was required at baseline to determine eligibility. To document the presence or absence of cCR, tumor assessments by PE and MRI were performed between the chemotherapy regimens (after the last dose of WP or *E* before initiating AC). Tumor assessment by PE was required following the last cycle of AC.

Criteria for PE assessment for clinical response between the two chemotherapy regimens and following the last cycle of chemotherapy (before surgery) included palpable lesion(s) identified at baseline being no longer palpable and no new lesions or other signs of disease progression (cCR). Patients who did not meet the criteria for cCR or progressive disease were graded as having clinical partial response/stable disease (PR/SD). Clinical progressive disease was defined as an increase of $\geq$20 % in the sum of the longest diameter in the breast and regional lymph nodes or progression of other clinical manifestations of disease.

Response criteria by MRI (between the two chemotherapy regimens) were as follows: complete response (CR) was defined as no significant enhancement on MR images; PR was defined as at least a 30 % decrease in the maximal diameter of the tumor; and non-response (NR) was defined as any response <30 % decrease.

pCR was determined by the local pathologist after examination of tissue (breast and nodes) removed at the time of surgery. pCR was defined as no histologic evidence of invasive tumor cells in the surgical breast specimen, axillary nodes, or sentinel nodes identified after neoadjuvant chemotherapy.

We assessed safety by PE, interim history, and laboratory assessment. AE assessment occurred before treatment with WP (on days 1, 8, 15, and 22) or *E* (day 1 and 8), and before starting the every 3 week AC regimen. AE reporting was assessed according to the National Cancer Institute Common Terminology Criteria for Adverse Events (NCI CTCAE) version 4.0. Patient safety and reported AEs were continuously monitored and reviewed by the NSABP Foundation medical review team.

Statistical analysis

The primary aim of this study was to determine the rate of pCR in the breast and nodes of patients with LABC who received upfront *E*. The rate of pCR in breast and nodes in neoadjuvant studies using similar eligibility criteria has ranged from 16 to 26 %, with HER2-negative and hormone-receptor-negative patients (triple-negative) having a higher pCR than HER2-negative hormone-receptor-positive patients. The threshold of interest in this trial was a rate of pCR breast and nodes in excess of 20 %. Specifically, the trial used a single-stage three-outcome design and required at least six patients of 30 (20 %) to reach pCR in the *E* arm to warrant further studies of eribulin in this setting [21].

Results

Patient characteristics

Between January and August 2013, 50 patients with LABC met eligibility criteria and were randomly assigned to the study (19 patients to WP and 31 patients to *E*). One patient randomly assigned to *E* withdrew consent before receiving protocol therapy. Thus, 49 patients were evaluable for

efficacy and safety assessment. Patient characteristics are shown in Table 1. Median age was 48 (range 34–67 years) and 50 (range 28–70 years) for WP and *E*, respectively. Twenty-two patients had stage IIB, 16 had stage IIIA, nine had stage IIIB, and two had stage IIIC disease. Four patients had inflammatory breast cancer. Thirty-two were hormone-receptor positive, and 17 had triple-negative disease.

Compliance

On the WP ($N = 19$) arm, 17 patients completed all 4 cycles (12 doses), with two additional patients receiving 8 and 9 doses, respectively. On the *E* arm ($N = 30$), 28 patients completed all 4 cycles (8 doses), with one additional patient receiving 5 doses and another one receiving 2 doses. One dose-level reduction occurred with four patients on WP and with one patient on *E*. There were dose delays in five and four patients on WP and *E*, respectively. On the WP arm, 17 patients received 4 cycles of AC, an additional patient received 2 cycles, and another, who progressed on WP, received AC off study. On the *E* arm, 25 patients completed 4 cycles, and five other patients did not receive AC on protocol. Three patients progressed on *E*, one of whom underwent surgery at time of progression; two others received AC neoadjuvant treatment off study: one, because of a prolonged interruption of therapy for inter-current illness, who was treated off study with dose-dense AC, and another one who discontinued protocol therapy because of insurance coverage issues but received AC off study.

Response

Response data are summarized in Tables 2 and 3. A cCR by PE after WP or *E* was achieved in one and four patients, respectively. Progressive disease occurred during WP in one patient and in three receiving *E*. After completion of all neoadjuvant chemotherapy, a cCR was reported in eight of 17 patients on WP and 10 of 29 patients on *E*. Breast-conserving surgery was performed in six of 18 (33 %) women treated with WP and in eight of 28 (28 %) women receiving *E*.

Baseline and follow-up MRI results were available for 49 patients. By central review, 11 of 19 (58 %) in the WP arm had a response (10 PR and one CR) and 12 of 30 (40 %) in the *E* arm (11 PR and one CR). MRI results at the local institution were similar to those obtained in the central review.

The pathological response in breast and nodes was 26 % (5 of 19) on the WP arm and 17 % (5 of 30) on the *E* arm. The pCR in nodes with or without residual invasive disease in the breast was 42 % (8 of 19) with WP and 30 % (9 of 30) with *E*.

Table 1 Patient characteristics: NSABP FB-9

	No. of patients	
Characteristic	WP ($N = 19$)	*E* ($N = 30$)
Median age (range)	48 (34–67)	50 (28–70)
Performance status		
0	17	29
1	2	1
Tumor stage		
IIB	7	15
IIIA	6	10
IIIB	5	4
IIIC	1	1
Inflammatory	2	2
ER+/or PR+	11	21
ER− and PR−	8	9

WP weekly paclitaxel, *E* eribulin

Table 2 Response data after receiving weekly paclitaxel (WP) or Eribulin (*E*): NSABP FB-9

Response	WP (%)	*E* (%)
Clinical	($N = 18$)[a]	($N = 30$)[a]
CR	1 (5)	4 (13)
PR/SD	16 (88)	21 (70)
PD	1 (5)	3 (10)[b]
Missing	0	3 (10)
MRI (Central review)	($N = 19$)	($N = 30$)
CR	1 (5)	1 (3)
PR	10 (53)	11 (37)
Non-response	7 (37)	14 (47)
Missing	1 (5)	4 (13)
MRI (Investigator review)	($N = 19$)	($N = 30$)
CR	2 (11)	0
PR	12 (63)	11 (37)
Non-response	4 (21)	15 (50)
Missing	1 (5)	4 (13)

CR, complete response, *PR/SD,* partial response/stable disease

[a] Indicates palpable lesion at baseline

[b] One patient with PR/SD by physical examination had progressive disease by MRI

Safety

All patients who received any chemotherapy were evaluable for safety. AEs for laboratory and non-laboratory toxicities are summarized by regimen of therapy using the NCI CTCAE version 4.0. Table 4 lists grade 2–4 AEs that occurred during WP or *E*. No grade 5 AEs occurred. Table 5 lists the most common grade 3–4 toxicities occurring during the AC therapy. As anticipated, both WP

Table 3 Pathologic response data: NSABP FB-9

	WP ($N = 19$) (%)	E ($N = 30$) (%)
Pathologic response		
pCR breast and nodes	5 (26)	5 (17)
Triple negative	3 of 8 (37)	2 of 9 (22)
Hormone positive	2 of 11 (18)	3 of 21 (14)
pCR nodes	8 (42)	9 (30)
Inoperable (PD)	1 (5)	0

WP weekly paclitaxel, *E* eribulin, *pCR* pathologic complete response, *PD* progressive disease

Table 4 Most common grade 2–4 treatment-related toxicities with WP or *E*: NSABP FB-9

Adverse event	WP			*E*		
	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Neutropenia	2 (10.5)	0	0	2 (6.7)	4 (13.3)	1 (3.3)
Febrile neutropenia	0	0	0	0	1 (3.3)	0
Non-hematologic						
Fatigue	3 (15.8)	0	0	1 (3.3)	0	0
Nausea	2 (10.5)	0	0	4 (13.3)	0	0
Constipation	2 (10.5)	0	0	1 (3.3)	0	0
Diarrhea	2 (10.5)	1 (5.3)	0	1 (3.3)	0	0
Vomiting	2 (10.5)	0	0	1 (3.3)	0	0
Neuropathy						
Sensory	2 (10.5)	0	0	1 (3.3)	0	0
Motor	0	0	0	1 (3.3)	0	0

WP weekly paclitaxel, *E* eribulin

Table 5 Most common grade 3–4 treatment-related toxicities during AC: NSABP FB-9

Adverse event	After WP			After *E*		
	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)	Grade 2 (%)	Grade 3 (%)	Grade 4 (%)
Hematologic						
Neutropenia	0	3 (15.8)	6 (31.6)	1 (3.3)	2 (6.7)	3 (10.0)
Febrile neutropenia	N/A	1 (5.3)	0	N/A	1 (3.3)	0
Non-hematologic colitis						
Stomatitis	0	1 (5.3)	0	0	0	0
Fatigue	0	1 (5.3)	0	0	0	0
	0	1 (5.3)	0	0	0	0

AC, doxorubicin and cyclophosphamide

and *E* regimens were well tolerated. With WP, the only grade 3 toxicity was diarrhea in one patient; no grade 4 toxicities were reported. With *E*, one patient had grade 4 neutropenia, and one patient experienced an episode of febrile neutropenia. Grade $\geq$3 peripheral neuropathy was not reported with either WP or *E*. Grade 2 peripheral neuropathy was reported in two patients on WP and two on *E*. One dose-level reduction occurred in four patients on WP and one on *E*. The significant lack of neurotoxicity with *E* in previously untreated patients was an important observation of this study. Seventeen of 19 (89 %) patients on WP received 12 doses and 28 of 30 (93 %) on *E* completed 4 cycles. AC was well tolerated following both WP and *E* regimens. The grade 3–4 toxicities (largely hematologic) were reported in nine patients who had received WP, one of whom experienced grade 3 febrile neutropenia. With *E*, five patients had grade 3–4 neutropenia, one of whom had grade 3 febrile neutropenia. Thus, there did not

appear to be any accumulative toxicity with either initial regimen (see Table 5).

Discussion

Interest in neoadjuvant therapy has increased since the United States Food and Drug Administration (US FDA) proposed in June 2012 to grant accelerated approval to neoadjuvant therapy for breast cancer patients based on the surrogate endpoint of pCR [22]. In a meta-analysis from 12 international neoadjuvant trials and 11,955 patients [23], the association between pCR and long-term outcomes were strongest in triple-negative patients and in HER2-positive, receptor-negative patients. The first such approval for neoadjuvant therapy in LABC occurred on September 30, 2013, with the inclusion of pertuzumab for use as neoadjuvant therapy in combination with trastuzumab and docetaxel in women with HER2-positive breast cancer [24].

Based on the phase II objective response rates with *E* in heavily pretreated patients and the survival advantage demonstrated in the phase III trial in advanced disease comparing *E* with physicians' choice, our study aimed to evaluate efficacy of the therapy as determined by pCR from sequential *E* followed by AC in patients with HER2-negative locally advanced disease [18–20]. We randomly assigned patients in a 1:2 ratio to either WP followed by AC or to *E* followed by AC, not as a direct comparator but rather to determine that the study population was consistent with those of earlier studies reported in the literature. With WP, pCR in breast and nodes was achieved in five of 19 patients (26 %). This is similar to the 28 % pCR reported in a larger MD Anderson study ($N = 131$) with WP followed by FEC [25]. Treatment with *E* in our study resulted in a pCR in breast and nodes in five of 30 patients (17 %). Although the number of patients with triple-negative disease was small in both arms, the pCR was three in eight with WP and two in nine with *E*.

The lack of any notable differences in clinical responses, MRI responses, and rates of breast-conserving surgery between the WP or *E* regimens is consistent with the pCR findings. The number of patients who achieved pCR for *E* was below our threshold for additional study. A potential weakness of this study is that only 4 cycles (8 doses) of *E* were planned in 85 days before AC was initiated. Whether a higher pCR might have been achieved with additional upfront cycles of *E* and to what extent additional toxicities would have become manifest is speculative. It is noteworthy that three patients were reported to have disease progression during or upon completion of *E*.

In summary, substitution of *E* for WP as administered in this study did not suggest increased pCR in HER2-negative LABC. Further study of *E* with this dose schedule in the neoadjuvant setting does not appear to be warranted.

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