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Phase I–II study of the farnesyl transferase inhibitor tipifarnib plus sequential weekly paclitaxel and doxorubicin–cyclophosphamide in HER2/neu-negative inflammatory carcinoma and non-inflammatory estrogen receptor-positive breast carcinoma

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Abstract

Tipifarnib (T) is a farnesyl transferase inhibitor (FTI) that enhances the antineoplastic effects of cytotoxic therapy in vitro, has activity in metastatic breast cancer, and enhances the pathologic complete response (pCR) rate to neoadjuvant doxorubicin–cyclophosphamide (AC) chemotherapy. We, therefore, performed a phase I–II trial of T plus neoadjuvant sequential weekly paclitaxel and 2-week AC chemotherapy in locally advanced breast cancer. Eligible patients with HER2-negative clinical stage IIB–IIIC breast cancer received 12 weekly doses of paclitaxel (80 mg/m^2) followed by AC (60/600 mg/m^2 every 2 weeks and filgrastim), plus T (100 or 200 mg PO on days 1–3 of each P dose, and 200 mg PO on days 2–7 of each AC cycle). The trial was powered to detect an improvement in breast pCR rate from 15 to 35 % ($\alpha = 0.10$, $\beta = 0.10$) in two strata, including ER and/or PR-positive, non-inflammatory (stratum A) and inflammatory carcinoma (stratum B). Of the 60 patients accrued, there were no dose-limiting toxicities among the first six patients treated at the first T dose level (100 mg BID; $N = 3$) or second T dose level (200 mg BID; $N = 3$) plus paclitaxel. Breast pCR occurred in 6/33 patients (18 %, 95 % confidence intervals (CI) 7–36 %) and 1/22 patients (4 %, 95 % CI 0–8 %) in stratum B. Combination of the FTI T with weekly paclitaxel–AC is unlikely to be associated with a breast pCR rate of 35 % or higher in patients with locally advanced HER2/neu-negative inflammatory or non-inflammatory ER- and/or PR-positive breast carcinoma.

Keywords

Farnesyl transferase inhibitor; Tipifarnib; Ras; Breast cancer; Neoadjuvant chemotherapy; Inflammatory breast cancer

Introduction

Although the frequency of *ras* mutations in breast cancer is low (<2 %) [1, 2], hyper-activation of Ras pathway is common due to signaling upstream from epidermal growth factor receptors and/or human epidermal growth factor-2 (HER-2/*neu*) [3, 4] or activation of estrogen-dependent pathways [5]. Ras protein overexpression is associated with poor

prognosis [6], and RhoC overexpression (a downstream effector of Ras) is associated with regional and/or distant metastases [7], and with inflammatory breast carcinoma [8].

Protein farnesyl transferase inhibitors (FTIs) were originally designed to target the Ras signal transduction pathway, although several other intracellular proteins are also dependent on post-translational farnesylation for their function [9, 10]. FTIs cause accumulation of cells in G2/M phase or G1 phase [10–13], induce apoptosis of a variety of tumor cell lines irrespective of *ras* mutation status [14], inhibit angio-genesis [15], inhibit growth of MCF-7 human breast cancer xenografts (which have wild-type Ras) [16], induce tumor regression in breast cancer transgenic mouse models [17, 18], augment the effect of antitubulin agents such as paclit-axel [19–22], and revert the RhoC GTPase-induced inflammatory breast cancer phenotype [8]. Increased Ras/Raf-1/MEK/MAPK activity has been implicated in doxorubicin-resistant MCF-7 cell line [23], paclitaxel-resistant cells [24], and the expression of the P-glycoprotein extrusion pump [25]. Tipifarnib (T) is an orally available FTI (formerly R115777; Zarnestra™, Johnson & Johnson, PRD, LLC, Raritan, NJ & Tibotec Therapeutics, Raritan, NJ) that produces objective response in about 10 % of patients with metastatic breast cancer [26].

Based upon these considerations, we previously conducted a phase I/II trial of T in combination with preoperative dose-dense (every 2 week) doxorubicin and cyclophosphamide (AC) in patients with stage IV breast cancer (for the phase I trial) and clinical stage IIB–IIIC breast cancer (for the phase II trial). We observed that the FTI T inhibits farnesyltranferase enzyme activity in vivo in the primary breast cancers, is associated with downregulation of p-STAT3 expression and improved the breast pathologic complete response (pCR) rate to 25 % (from an expected 10 % based upon historical data) [27, 28]. The incremental improvement in breast pCR associated with AC–T combination was comparable to the effect of sequentially adding a taxane to AC (e.g., 27 % for AC–docetaxel vs. 13 % for AC alone in B27 trial) [29].

In order to further improve the breast pCR rates, we performed a phase I–II trial of T plus sequential weekly paclitaxel followed by every 2-week AC chemotherapy, which has been shown to produce high pCR rates when used in the neoadjuvant setting, and improved clinical outcomes when used in the adjuvant setting [30, 31]. We evaluated the effectiveness of this regimen in HER2/neu non-overexpressing tumors typically associated with low pCR rates, including non-inflammatory ER-positive carcinoma (stratum A) and inflammatory carcinoma irrespective of ER/PR expression (stratum B). The primary objective was to determine if the combination of T plus sequential weekly paclitaxel followed by dose-dense AC improved the breast pCR rates from 15 to 35 % in each stratum.

Methods

Patient selection

Patients were required to have histologically or cytologically confirmed adenocarcinoma of the breast, clinical stage IIB–IIIC, and HER2/neu non-overexpressing disease (0 or 1+ by immunohistochemistry, or non-amplified by fluorescent in situ hybridization). Other requirements included: (1) age ≥ 18 years, (2) ECOG performance status 0 or 1, (3) normal

organ and marrow function (leukocytes ≥ 3,000/μl, absolute neutrophil count ≥ 1,500/μl, platelets 100,000/μl, serum creatinine and total bilirubin within institutional normal limits, aspartate transaminase and/or alanine transaminase ≤2.5-fold above the institutional upper limit of normal, and left ventricular ejection fraction within normal institutional limits). The study was reviewed, approved, and sponsored by the Cancer Therapy Evaluation Program of the National Cancer Institute (NCI study number P7868, Clinical Trials.gov identifier NCT00470301). The protocol was reviewed by the local institutional review board at each participating institution, and all the patients provided written informed consent.

Paclitaxel plus tipifarnib therapy

Paclitaxel [80 mg/m^2 by intravenous (IV) infusion over 1 h] was given on day 1 weekly for up to 12 doses, preceded 30–60 min prior to each dose by premedication with dexamethasone (10 mg IV prior to the first paclitaxel dose, and 4 mg prior to each subsequent dose), diphenhydramine (25–50 mg or equivalent), and an H-2 blocker (ranitidine 50 mg IV or equivalent). T was given at a dose of 100 or 200 PO twice daily on days 1–3 of each weekly paclitaxel dose, and treatment with paclitaxel/T was given if the neutrophil count was at least 1,000/μl, platelet count at least 100,000/μl, and adequate recovery from non-hematologic toxicity (to grade 0–1, or grade 0–2 for neuropathy). Continuation of paclitaxel was permitted with a 25 % dose reduction if there was grade 2 neuropathy, and held and reduced in subsequent cycles for grade 3–4 neuropathy.

AC plus tipifarnib therapy

Following completion of paclitaxel–T, patients received doxorubicin (60 mg/m^2 by slow IV push over 10–15 min) and cyclophosphamide (600 mg/m^2 by IV infusion over 30–60 min) given on day 1 every 2 weeks for up to four cycles, preceded by the standard anti-emetic therapy. T was given at a dose of 200 mg BID on days 2–7 of each AC treatment cycle. Treatment cycles were repeated if the neutrophil count was at least 1,500/μl, platelet count at least 100,000/μl, and if there was adequate recovery from non-hematologic toxicity (to grade 0–1). All patients also received granulocyte colony-stimulating factor; 5 mg/kg subcutaneously on days 2–13 of each AC cycle (pegfilgrastim was not used).

Tipifarnib dose escalation

The T dose (100 or 200 mg) was escalated in cohorts of 3–6 patients based upon toxicity that occurred in the first 4 weeks of therapy of weekly paclitaxel. Dose-limiting toxicity (DLT) during cycle 1 was defined as: (a) febrile neutropenia (grade 3 or 4), (b) grade 3–4 thrombocytopenia, (c) grade 3–4 non-hematologic toxicity (or any grade 5 toxicity) attributed to chemotherapy (nausea, vomiting was considered dose-limiting only if not controlled with adequate anti-emetic therapy), and (d) omission of one or more paclitaxel doses due to toxicity. The recommended phase II dose was defined as the dose level at which 0/3 or 1/6 had a DLT, or one dose level below which >/2 of 3 or >/2 of 6 had a DLT.

Surgery and post-protocol therapy

Patients were re-assessed for surgery following the fourth cycle of AC. All patients with an operable primary breast cancer who were candidates for surgery underwent mastectomy or

lumpectomy plus sentinel node biopsy and/or axillary dissection about 4 weeks after completion of the last cycle of AC. After surgical resection, patients received endocrine therapy (tamoxifen or an aromatase inhibitor) for at least 5 years, and chest wall/regional node irradiation if there were indications for radiation (e.g., inflammatory carcinoma, tumor size >5 cm, and 1 or more positive axillary nodes).

Protocol-required studies, response criteria, and toxicity grading

All patients underwent computerized tomography of the chest and abdomen, bone scan, and bilateral mammogram within 8 weeks of registration; and nuclear cardiac scan or echo-cardiogram for estimation of left ventricular ejection fraction within 12 weeks of registration. Clinical tumor response was assessed by physical examination by the treating physician after completion of therapy. Complete clinical response was defined as complete resolution of the breast mass and adenopathy or skin changes (if present), and partial clinical response was defined as a 30 % reduction in the sum of the longest unidimensional measurement [32]. Toxicity was graded according to the National Cancer Institute Common Terminology for Adverse Events, Version 3.0.

Pathology review

Pathological response was assessed by the local pathologist using procedures normally utilized for evaluation of surgical breast cancer specimens; breast pCR was defined as no evidence of invasive carcinoma in the breast. Pathologic responses were reviewed for “residual cancer burden” (RCB) score as described by Symmans et al. [33] at MD Anderson Cancer Center by one of the co-authors who is a breast pathologist (SF) for patients treated at Montefiore ($N = 20$), or by breast pathologists at the UT. MD Anderson Cancer Center ($N = 18$, all in stratum B) or the four other participating centers ($N = 22$) who were asked to complete a case report form documenting review by RCB scoring criteria.

Statistical considerations

The primary objective of the phase I trial was to determine the recommended phase II dose of T when combined with weekly paclitaxel. The primary objective of the phase II trial was to determine the breast pCR rate. A co-primary objective of the phase I and II trials was to evaluate the feasibility and safety of the combination. The study was designed to detect an increase in the breast pCR rate from ≤15 % (anticipated for chemotherapy alone) to at least 35 % ($\alpha = 0.05$, $\beta = 0.10$) using Simon's two-stage design in each stratum. If three or fewer breast pCRs were observed among the initial 19 evaluable patients in each stratum, accrual to that stratum was terminated early and declared negative; if at least four breast pCRs were observed, accrual would continue to an additional 14 evaluable patients in each stratum (for a total of 33 patients). If at least eight pCRs were observed among the 33 evaluable patients, this regimen would be considered worthy of further testing in this population.

Results

Patient characteristics

A total of 60 patients were enrolled from six centers between April 2007 and April 2011. A total of seven patients were enrolled in the phase I portion of the trial, including four patients

at the first T dose level (one of whom withdrew prior to completing the first treatment cycle and was replaced), and three patients at the second and final T dose level. Of the three patients treated at the second dose level, two patients were included in the efficacy analysis for the phase II trial, including one patient in stratum A and one patient in stratum B (the third patient at the second dose level had ER/PR-negative, non-inflammatory disease and thus not eligible for inclusion in stratum A or B). The characteristics of the 55 patients eligible for efficacy evaluation in phase II trial are shown in Table 1, including 33 patients in stratum A and 22 patients in stratum B. The median age was 50.4 and 54.5 years for patients in stratum A and B, respectively. Twenty-one of 33 patients (64 %) patients in stratum A had stage III A disease or higher, and all 22 patients in stratum B had stage IIIB disease or higher.

Results of dose escalation

There were no DLTs in the first six evaluable patients treated at dose level 1 (100 mg BID) and 2 (200 mg BID); the recommended phase II dose of T was 200 mg BID on days 1–3 of each paclitaxel dose.

Treatment administered

Of the 60 patients treated in the phase II trial, patients were planned to receive a maximum of 720 paclitaxel doses and 220 cycles of AC. Regarding delivery of paclitaxel, at least 10 paclitaxel doses were given to 57 patients (95 %), and all 12 paclitaxel doses were given to 44 patients (73 %), including 681 paclitaxel doses given at full dose (95 % of 720 planned doses) and 11 paclitaxel doses (2 %) given at a reduced dose in 2 patients. T was given with 633 of 692 paclitaxel doses given (91 %), and in all cycles in 44 patients (73 %), and only two patients (4 %) received less than four cycles of the AC–T combination. The most common reason for reducing or omitting T included gastrointestinal side effects (nausea/dyspepsia).

Adverse events

The worst-grade adverse events coded as grade 2 or higher observed at the recommended phase II dose are shown in Table 2. The most common grade 3–4 adverse events occurring in at least 5 % of patients included neutropenia in 21.7 %, anemia in 8.4 %, nausea in 10 %, vomiting in 6.7 %, pain in 6.7 %, diarrhea in 5 %, and fatigue in 5 %. There were no treatment-associated deaths.

Pathological response

Pathologic response data for the phase II trial are summarized in Table 3. There were four breast pCRs among the first 19 evaluable patients in the first stage of accrual to stratum A, thereby meeting criteria for accrual to the second stage. However, breast pCR occurred in 6 of 33 patients overall in stratum A (18 %, 95 % confidence intervals (CI) 7–36 %), which was insufficient to declare the regimen promising. Of the 22 total patients in stratum, there was one breast pCR (4 %, 95 % CI 0–8 %), which was insufficient to proceed to the second stage. All patients is stratum A proceeded to surgery, whereas three patients in stratum B did not have surgery because of progressive disease (N-2) or death due to an unrelated cause

(N-1; accidental death). Residual cancer burden (RCB) scores are also shown for each stratum, indicating in an intention to treat analysis that 6 of 33 patients (18 %) in stratum A had an RCB score of 0–1, and 4 of 22 patients (18 %) in stratum B. Of the five patients in the phase I trial assigned to either 100 mg ($N = 4$) or 200 mg ($N = 2$) of T, two of four patients with ER/PR-negative disease had an RCB score of 0–1 (including an inflammatory cancer with an RBC of 0), whereas a single patient with ER-/PR-positive inflammatory cancer had an RCB score of 3.

Discussion

Pathologic complete response in the breast (or breast and lymph nodes) after neoadjuvant chemotherapy is a short-term surrogate endpoint known to be associated with reduced risk of recurrence and breast cancer death [33–36]. The U.S. Food and Drug Administration has recently recognized pCR as an acceptable surrogate endpoint supporting accelerated drug approval if of sufficient magnitude, and supporting regular approval if subsequently accompanied by longer followup to establish that higher pCR rates translate into improved disease-free survival [37]. Relying on pCR rate as the primary trial endpoint to evaluate novel agents in combination with the standard neoadjuvant chemotherapy has been advocated as an innovative phase II clinical trial model for identifying the most promising agents to study in more definitive phase I–II adjuvant and neoadjuvant trials [38]. Our objective in this trial was to determine whether addition of T would improve the breast pCR rate from 15 % or less to at least 35 %, an absolute improvement that may translate into clinical benefit [39].

In a previous study, we had shown that T (200 mg PO BID) produced at least 90 % intratumoral FTase enzyme inhibition in vivo, was associated with relatively high breast pCR rates when combined with four cycles of dose-dense AC chemotherapy (25 %), and did not compromise the ability to deliver AC due to added toxicity [27, 28]. In the current study, we sought to further enhance the efficacy of T–chemotherapy regimen to at least 35 % by combining T with sequential weekly paclitaxel followed by every 2-week AC chemotherapy. The premise underlying this is supported by evidence indicating that FTIs enhance the antineoplastic effects of taxanes [19–22], the efficacy of weekly neoadjuvant paclitaxel irrespective of hormone receptor expression [30, 31]; and other similar trials that used an identical backbone chemotherapy [40]. We evaluated the efficacy of this regimen in populations known to have low (<10–15 %) breast pCR rates, including patients with HER/neu non-overexpressing disease that is ER- and/or PR-positive (stratum A) [41]. We also evaluated this combination in patients with inflammatory breast carcinoma (stratum B) because pCR rates are also low in this setting, and FTIs revert the RhoC GTPase-induced inflammatory breast cancer phenotype [8].

Despite the strong rationale supporting this study, the primary efficacy endpoint was not met, indicating that the combination of T plus sequential paclitaxel–AC chemo-therapy is unlikely to produce a breast pCR rate of at least 35 % in each stratum evaluated. Despite the positive signal in the prior trial of the T–AC combination in an unselected population, we found no evidence that T enhances pCR rates when combined with paclitaxel–AC in populations selected to have low pCR rates. pCR rates in ER-positive disease do not

correlate with disease recurrence and survival as in HER/neu-positive or triple negative disease [41]. Further followup will be required to determine whether patients with ER-positive disease treated with this combination will experience lower recurrence rates than expected, although the power to detect such differences is limited given the small sample size.

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Table 1

Characteristics of patient population in phase II portion of trial (N = 55)

Characteristics	Stratum A (N = 33) ER and/or PR-positive, non-inflammatory carcinoma	Stratum B (N = 22) inflammatory carcinoma
Median age (range)	50.4 years (33–76)	54.5 years (34–77)
ECOG PS		
0	28 (85 %)	19 (87 %)
1	5 (15 %)	3 (13 %)
Clinical stage		
Stage IIA–IIIA	31 (94 %)	0
Stage IIIB non-inflammatory	2(6%)	0
Stage IIIB inflammatory	0	16 (73 %)
Stage IIIC inflammatory	0	6 (27 %)
ER/PR expression[a]		
ER+/PR+	26 (79 %)	8 (36 %)
ER+/PR–	7 (21 %)	4 (18 %)
ER–/PR+	0	1 (5 %)
ER–/PR–	0	9 (41 %)
Menopausal status		
Pre/peri-menopausal	18 (55 %)	8 (36 %)
Postmenopausal	15 (45 %)	14 (64 %)

[a] ER/PR expression coded as per ASCO-CAP guidelines

Table 2

Grade 2–4 adverse events associated with therapy in all treated patients (N = 60)

Adverse events	Grade 2 *n* (%)	Grade 3 *n* (%)	Grade 4 *n* (%)
Hematologic			
Anemia	29 (48.3)	4 (6.7)	1 (1.7)
Neutropenia	16 (26.7)	7 (11.7)	6 (10)
Lymphopenia	3 (5)	3 (5)	0
Non-hematologic			
Fatigue	28 (46.7)	3 (5)	0
Nausea	11 (18.3)	6 (10)	0
Vomiting	6 (10)	4 (6.7)	0
Diarrhea	13 (21.7)	3 (5)	0
Sensory neuropathy	18 (30)	2 (3.3)	0
Pain	11 (18.3)	4 (6.7)	0
Skin rash	11 (18.3)	3 (5)	0
Nail changes	10 (16.7)	0	0
Hyperglycemia	8 (13.3)	1 (1.7)	1 (1.7)
Hypoglycemia	6 (10)	0	0
Infection[a]	8 (13.3)	1 (1.7)	0

[a] Infection associated with the normal absolute neutrophil count

Table 3

Response to therapy in phase II trial ($N = 55$)

	Stratum A ER and/or PR-positive non-inflammatory carcinoma	Stratum B inflammatory carcinoma
No. of patients	33	22
Number of breast pCR (% and 95 % CI)	6 (18 %; 95 % CI 7–36 %)	1 (4 %; 95 % CI 0–8 %
Number of breast and axillary node pCR (% and 95 % CI)	5 (15 %; 95 % CI 3–27 %)	1 (4 %; 95 % CI 0–8 %)
Residual cancer burden (RCB)		
0	5 (15 %)	1 (4 %)
1	1 (3 %)	3 (14 %)
2	14 (42 %)	9 (41 %)
3	11 (33 %)	6 (27 %)
Surgery done, not evaluated	2(6%)	0
Surgery not performed	0	3 (14 %)