original article

Annals of Oncology 20: 449–453, 2009
doi:10.1093/annonc/mdn661
Published online 15 December 2008

Phase II trial of weekly nab (nanoparticle albumin-bound)-paclitaxel (nab-paclitaxel) (Abraxane®) in combination with gemcitabine in patients with metastatic breast cancer (N0531)

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Received 25 August 2008; accepted 3 September 2008

Nanoparticle albumin-bound (nab)-paclitaxel has better efficacy and practically eliminates the risk of hypersensitivity reactions associated with solvent-based paclitaxel. We studied weekly nab-paclitaxel and gemcitabine combination in an open-label one-stage, phase II trial in patients with previously untreated metastatic breast cancer (MBC). Nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) were administered on days 1 and 8 of a 21-day cycle until disease progression. Fifty patients were enrolled. Forty (80%) had visceral organ involvement and 30 (60%) had ≥ 3 sites of metastases. Four (8%) and 21 (42%) patients had complete and partial responses by Response Evaluation Criteria in Solid Tumors (RECIST) criteria. Median duration of response was 6.9 months [95% confidence interval (CI) 5.7, not reached], median progression-free survival (PFS) 7.9 months (95% CI 5.4–10 months), and median overall survival (OS) was not reached. PFS and OS at 6 months were 60% (95% CI 48% to 76%) and 92% (95% CI 85% to 100%), respectively. Therapy was well tolerated. Neutropenia was commonest toxicity (42% and 12% grades 3 and 4 neutropenia). Only one patient developed febrile neutropenia. Significant activity and favorable toxicity profile provides a basis for considering this regimen for further evaluation in phase III trials or in combination with biologic agents.
Key words: breast cancer, chemotherapy, gemcitabine, nab-paclitaxel

introduction

Paclitaxel is a tubulin-stabilizing chemotherapeutic agent with proven efficacy against breast cancer. The poor solubility of paclitaxel requires the use of the lipid-based solvent polyoxyl castor oil (Cremophor EL; BASF, Ludwigshafen, Germany) as a vehicle, which can cause histamine-mediated hypersensitivity reactions. Despite the use of prophylactic antihistaminic agents and corticosteroids, severe or even fatal reactions can still occur. Additionally, cremophor-containing preparations of paclitaxel have to be infused through specialized non-di(2-ethylhexyl) phthalate-containing infusion sets with inline filters over 1–3 h depending on the dose. Preclinical data suggest that cremophor may also alter the pharmacodynamics and free drug availability of paclitaxel [1].

Nanoparticle albumin-bound paclitaxel (nab-paclitaxel) is a solvent-free formulation in which paclitaxel is delivered as a suspension of albumin nanoparticles (average size 130 nm) eliminating the need for premedication or special infusion sets and allowing infusion to be safely given over 30 min. Additionally, drug transport into tumors may be enhanced by albumin receptor and caveolae-mediated transport across endothelial cells [2]. In preclinical as well as clinical studies, nab-paclitaxel has been shown to have significantly reduced acute toxicity and in at least in one randomized trial, superior efficacy to solvent-based paclitaxel. Response rate in patients with MBC was almost doubled (33 versus 19%; $P = 0.001$) with three-weekly nab-paclitaxel (260 mg/m^2) compared with paclitaxel (175 mg/m^2). This was associated with improved time to progression (TTP) (23 versus 16.9 weeks; $P = 0.006$) and a trend for greater median survival [3]. The risk of peripheral neuropathy was higher with nab-paclitaxel in this trial (10% versus 2% grade 3 sensory neuropathy), likely because of higher total dose of paclitaxel in the nab-paclitaxel arm. Weekly schedule of nab-paclitaxel has also been evaluated and a 30-min infusion without premedications is very well tolerated [4]. A dose of 100 mg/m^2 over 30 min on days 1, 8, and 15 on a 28-day cycle was evaluated in a phase II study by Blum et al. for patients with taxane refractory MBC. Overall response rate [partial response (PR)] was 15%, and disease control rate [PR + stable disease (neither sufficient shrinkage to

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qualify for Partial Response (PR) nor sufficient increase to qualify for Progressive Disease (PD)) (SD) ≥16 weeks] was 30%. Three-weekly nab-paclitaxel (300 mg/m^2) was compared with 100 or 125 mg/m^2 nab-paclitaxel every week or three-weekly docetaxel (100 mg/m^2) in a randomized phase II study for first-line therapy for MBC. Preliminary results suggest that weekly nab-paclitaxel may be more active than three-weekly nab-paclitaxel or docetaxel and a dose response for weekly nab-paclitaxel may exist [5].

Gemcitabine is a pyrimidine nucleotide antimetabolite that is phosphorylated intracellularly to active triphosphate, which inhibits DNA replication and RNA synthesis. Incorporation of gemcitabine triphosphate in the DNA makes it resistant to exonuclease excision, leading to apoptosis. Gemcitabine has activity in a wide variety of malignancies including breast cancer. Preclinical studies have shown evidence of synergism with paclitaxel in the form of increased incorporation of gemcitabine metabolites in the RNA, G0/G1 growth arrest, increased apoptosis, and more potent inhibition of tumor growth with paclitaxel–gemcitabine (PG) combination than either agent alone [6, 7]. A phase III study of gemcitabine and paclitaxel (GT) combination demonstrated superior antitumor activity in anthracycline-pretreated patients with MBC with an overall response rate (RR) of 39%, compared with paclitaxel alone (RR 25%), consistent with the positive interaction demonstrated in preclinical models [8]. Interim results also demonstrated statistically significant improvement in TTP and overall survival (OS) with GT combination. There was a trend toward improved pain score, reduced analgesic use, and increased overall quality of life in the GT group [9].

The proven efficacy of GT combination and the potential advantages of nab-paclitaxel led us to investigate the combination of nab-paclitaxel and gemcitabine for MBC. We conducted a phase II trial of this combination administered weekly for 2 weeks in a 21-day cycle for treatment of patients with previously untreated MBC.

patients and methods

patient eligibility

An open-label, multicenter phase II trial was conducted through the North Central Cancer Treatment Group. Twenty-two centers in the United States accrued 50 patients from November 2005 to May 2006. Patients over the age of 18 years with histologically or cytologically confirmed invasive breast cancer who had clinical evidence of metastatic disease were eligible. Other key eligibility criteria included measurable disease, adequate organ function, Eastern Cooperative Oncology Group performance status of zero to one, and no previous chemotherapy for metastatic disease. Patients may have received prior hormonal therapy for MBC. Therapy with a taxane as part of adjuvant or neo-adjuvant therapy was allowed but must have been completed at least 6 months before study entry. Patients with active central nervous system metastasis or with more than grade 1 peripheral neuropathy were ineligible. The study was approved by the Institutional Review Board of all the participating institutions and all patients gave informed written consent before entry into the trial.

study design

Nab-paclitaxel (125 mg/m^2) and gemcitabine (1000 mg/m^2) were administered on days 1 and 8 of every cycle. Cycles were repeated every 21 days until disease progression, unacceptable toxicity, or withdrawal of consent. Stepwise dose reductions in nab-paclitaxel (100 and 80 mg/m^2) and gemcitabine (800 and 600 mg/m^2) doses were done per protocol for toxicity. Treatment was delayed up to a maximum of 21 days if toxic effects had not resolved to less than grade 2. All patients received antiemetic prophylaxis per their physicians' discretion. Routine premedication with corticosteroid or antihistamines was not used.

statistical methods

A single-stage phase II trial design was used for this study. The primary end point was the proportion of confirmed responses, with a success being defined as a complete response (CR) or partial response (PR) according to RECIST criteria on two consecutive evaluations at least 6 weeks apart. A total of 41 assessable patients were required to test the null hypothesis that the true confirmed response rate is at most 40% versus the alternative that it is at least 60%. Assuming that the number of confirmed responses is binomially distributed, the study had 90% power, with a 10% type I error rate. A patient was considered assessable for response if they were eligible and received treatment. At least 21 responses were required in the first 41 assessable patients to conclude that this regimen is promising and may be recommended for further testing in this patient population. The proportion of confirmed responses was estimated by the number of patients who achieved a confirmed response divided by the total number of assessable patients. Ninety-five percent confidence intervals (CIs) were calculated for the true confirmed response rate using properties of the binomial distribution.

OS time was defined as the number of days from registration to the date of death or last follow-up. Progression-free survival (PFS) was defined as the number of days from registration to the date of disease progression or death, with patients who are alive and progression free being censored on the date of their last evaluation. If a patient died without documentation of disease progression, the patient was considered to have had tumor progression at the time of their death unless there was sufficient documented evidence to conclude no progression occurred before death. Duration of response is the number of days from the first date a response (CR or PR) was recorded to the date of progression or last follow-up. The distributions of time-to-event end points were estimated using the Kaplan–Meier method.

results

Fifty women were enrolled from 22 centers. Median age was 56 years (range 29–86). Forty patients (80%) had visceral disease. Tumors were estrogen receptor (ER) positive in 34 (68%), progesterone receptor (PR) positive in 28 (56%), and HER2 positive in one (2%) patient.

Patient characteristics are described in Table 1. Twenty-five (50%) patients had received prior adjuvant chemotherapy, including 15 (30%) who had received prior taxane therapy (seven paclitaxel, eight docetaxel). One patient (2%) had received trastuzumab as part of adjuvant therapy. At the time of this report, 38 (76%) patients are alive and 17 (34%) progression∼free. Median follow-up for survivors is 11 months (range 5–16). Median of seven cycles were administered (range 1–17). Forty four (88%) have discontinued therapy due to disease progression (43%), patient refusal (23%), adverse events (AEs) (18%) or alternate therapy (9%), intercurrent illness (2%), and other (5%). Confirmed response was noted in 25 (50%) patients (95% CI 36% to 64%), CR in four (8%), and PR in 20 (42%). Median duration of response was

Table 1. Patient characteristics ($n = 50$)

Median age	56 years (range 29–86)
Performance score	
0	23 (46%)
1	27 (54%)
Dominant disease site	
Soft tissue	5 (10%)
Osseous	4 (8%)
Visceral	41(82%)
No. of metastatic sites	
1	5 (10%)
2	15 (30%)
3+	30 (60%)
Estrogen/progesterone receptor expression	
Positive	34 (68%)/28 (56%)
Negative	14 (28%)/20 (40%)
Unknown	2 (4%)/2 (4%)
HER2 status	
Positive	1 (2%)[a]
Negative	49 (98%)
Prior chemotherapy	25 (50%)
Anthracycline	24 (48%)
Taxane; paclitaxel/docetaxel	15 (30%); (7/8)

[a]Patient had prior trastuzumab.

Table 2. Grade 3 or more AEs occurring in >5% of patients ($n = 50$)

	Grade 3 (%)	Grade 4 (%)	Total (%)
Neutropenia	21 (42%)	6 (12%)	27 (54%)
Fatigue	14 (28%)	0	14 (28%)
Anemia	7 (14%)	0	7 (14%)
Dyspnea	7 (14%)	0	7 (14%)
Thrombocytopenia	5 (10%)	1 (2%)	6 (12%)
Arthralgia	4 (8%)	0	4 (8%)
Vomiting	4 (8%)	0	4 (8%)
Neuropathy	4 (8%)	0	3 (6%)
Myalgia	3 (6%)	0	3 (6%)
Nausea	3 (6%)	0	3 (6%)
Pain—abdominal	3 (6%)	0	3 (6%)
AST	3 (6%)	0	3 (6%)

AE, adverse event; AST, aspartate aminotransferase.

6.9 months (95% CI 5.7, not reached). Median PFS (PFS) was 7.9 months (95% CI 5.4–10 months). Median OS was not reached. Rate of PFS and OS at 6 months was 60% (95% CI 48% to 76%) and 92% (95% CI 85% to 100%), respectively.

All 50 patients were assessable for toxicity. Overall, therapy was generally well tolerated and was managed on an outpatient basis in the majority of patients. The majority of severe AEs were hematologic. Grade 3 or 4 neutropenia occurred in 27 (54%) patients, anemia in seven (14%), and thrombocytopenia in six (12%). Neutropenia was generally uncomplicated and managed as outpatient. Only one patient (2%) had febrile neutropenia. Median white blood cell nadir was 1.90×10^9/l and median platelet nadir was 199×10^9/l. Other grades 3–4 AEs included fatigue in 14 (28%), dyspnea in seven (14%), and grade 3 peripheral neuropathy in four (8%). Thirty-three patients required dose delays in a total of 68 cycles, mostly due to hematologic AEs. Dose reduction was required in 29 patients in 53 cycles, mostly due to hematologic AEs. Median dose delivered for nab-paclitaxel and gemcitabine was 125 and 1000 mg/m^2, respectively. Details of all grades 3–4 AEs are that occurred in >5% of patients is described in Table II.

discussion

In this phase II multicenter trial for treatment of patients eligible to receive first-line chemotherapy for metastatic breast cancer, we show that the nab-paclitaxel and gemcitabine combination has significant activity with excellent toxicity profile. Approximately a third of patients in our trial had previously received a taxane as part of adjuvant therapy. Confirmed response rate of 50% (8% CR and 42% PR) was noted with median duration of response of 6.9 months (95% CI 5.7, not reached), median PFS of 7.9 months (95% CI 5.3–9.3), and rate of OS at 6 months of 91% (95% CI 84% to 100%). Median OS was not reached. The regimen was well tolerated. No hypersensitivity reactions were encountered despite lack of routine use of corticosteroid or antihistamine premedications. The incidence of febrile neutropenia was low (one patient, 2%). Only four (8%) patients in our cohort experienced maximum grade 3 neurotoxicity. Neuropathy improved to ≤grade 1 within one cycle in two patients who were then able to continue treatment after nab-paclitaxel dose reduction. The other two patients discontinued treatment because of neuropathy.

These results compare favorably to other treatments commonly used for treatment of anthracycline-pretreated MBC. An overall RR of 42%, median TTP of 6.1 months, and median survival of 14.5 months were seen with capecitabine and docetaxel combination in a phase III trial for treatment of anthracycline-pretreated patients with MBC [10]. This regimen was associated with grade 3 and four AEs in 71% and 25% patients, respectively. Combination of GT for first-line treatment of anthracycline-pretreated, taxane-naive MBC patients was associated with an RR of 39.3% and 6 month PFS of ∼50% [8, 9]. GT regimen was associated with longer TTP, an OS advantage, and better global Quality of Life score compared with three-weekly paclitaxel alone [11]. On the basis of these data, GT received regulatory approval by the Food and Drug Administration and is a widely used front-line regimen for MBC after prior anthracycline adjuvant therapy.

Paclitaxel was administered in a three-weekly schedule in the GT regimen [9]. Weekly dosing of paclitaxel has been shown to be better tolerated and more effective than three-weekly dosing [12, 13]. Studies show that weekly dosing of nab-paclitaxel is feasible, and preliminary data suggest better activity than three-weekly dosing [3, 4]. We developed the current study with the goal of improving on the efficacy of GT by harnessing the better therapeutic index of nab-paclitaxel and utilizing a weekly administration schedule. Although cross-study comparisons are not possible, our data are encouraging and compare favorably to GT and other commonly used first-line regimens for anthracycline-pretreated MBC.

Fifteen (30%) of patients in our study had previously received a taxane. There was no difference in responses based on prior taxane use. Better activity of nab-paclitaxel over solvent-based paclitaxel [3] and its activity in taxane-pretreated patients [4, 14] are likely related to enhanced drug delivery. Animal xenograft studies show that albumin-bound formulation of paclitaxel is distributed more rapidly into the tumor tissues [15]. Albumin is the natural transporter of hydrophobic molecules. The nab-paclitaxel complex is transported across the endothelium into the tumor interstitium via molecular pathways involving specific albumin receptor (gp60, albondin) and caveolin-1. Caveolin is the principal structural protein of caveolae, sphingolipid, and cholesterol-rich invaginations of the plasma membrane involved in vesicular trafficking and signal transduction [16]. Elevated expression of caveolin-1 has been documented in various tumor types, including breast cancer, and correlated with tumor aggressiveness and poor prognosis [17]. High expression of caveolin has also been associated with basal-like phenotype in sporadic and hereditary breast cancer [18]. Thus, one can theorize that nab-paclitaxel may be particularly active against BC with basal-like phenotype. An unplanned subgroup analysis of patients with ER/PR and HER2-negative (triple-negative) breast cancer in our cohort found that 10 of 13 (77%, 95% CI 46% to 95%) such patients had a response compared with 16 of 36 other patients (44%, 95% CI 28% to 62%). Limited conclusions are possible because of small patient numbers and *post hoc* subgroup analysis, but these data suggest the possibility that basal-like breast cancer may particularly responsive to nab-paclitaxel-containing regimen. This hypothesis can be tested in future studies.

Other molecules such as caveolin-2, SPARC (secreted protein, acidic and rich in cysteine), cortactin, and dynamin 2 involved in the internalization of albumin may also be important in determining patient response (and outcome) to nab-paclitaxel [19, 20]. Exploratory studies are ongoing to identify biologic correlates of response, which may allow prospective identification of patients who are most likely to benefit.

In conclusion, weekly nab-paclitaxel and gemcitabine combination demonstrated substantial activity and manageable toxicity as first-line therapy of MBC. These encouraging data and the favorable therapeutic index of nab-paclitaxel support the evaluation of this regimen in randomized phase III trials as first-line regimen for patients with metastatic breast cancer. Further improvement may be possible with the addition of biologic agents, such as antiangiogenic agents. Combination of paclitaxel and bevacizumab has been shown to result in improved PFS in MBC [21]. Our data build on the proven efficacy of a solvent-based paclitaxel and gemcitabine regimen and provides a rationale for testing nab-paclitaxel, gemcitabine, and an antiangiogenic agent in future clinical trials.

funding

Public Health Service (CA-25224, CA-37404, CA-15083, CA-63848, CA-35195, CA-35090, CA-35101, CA- 35269, CA-37417, CA-63849, CA-35272, CA- 35113, CA-60276, CA-35103, CA-35415, and CA-35431) from National Cancer Institute, Department of Heath and Human Services.

acknowledgements

This study was conducted as a collaborative trial of the North Central Cancer Treatment Group and Mayo Clinic. Research grants and study drug supplies were provided by Eli Lilly, Inc., and American Bioscience, Inc

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