Therapeutic Efficacy of a Novel Nanosomal Docetaxel Lipid Suspension Compared With Taxotere in Locally Advanced or Metastatic Breast Cancer Patients

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Abstract

Drug delivery systems are widely used to reduce toxicity of drugs and enhance the quality of a patient’s life. Nanosomal docetaxel lipid suspension (NDLS) is formulated based on an aqueous lipid delivery system. Patients with breast cancer were not required to be premedicated before administration of NDLS. Docetaxel administered using this delivery system also improves the response rate compared with commercially available docetaxel drug.

Background: Nanosomal docetaxel lipid suspension formulation was developed to eliminate ethanol and polysorbate 80 from the currently used docetaxel (Taxotere) drug for treatment of cancer patients. NDLS clinical safety and efficacy was evaluated and compared with Taxotere at 75 mg/m² in metastatic breast cancer patients. Patients and Methods: A total of 72 patients were randomized in a ratio of 2:1 (NDLS:Taxotere). Patients treated with NDLS were not premedicated with corticosteroids as required with solvent-based Taxotere. Disease status and tumor response was assessed after every 2 cycles of treatment using Response Evaluation Criteria in Solid Tumors 1.1 guidelines through cycle 6. Results: Overall therapeutic response (complete + partial) rate in metastatic breast cancer patients treated with NDLS and Taxotere were 35.5% and 26.3%, respectively, indicating better response in patients treated with NDLS. Patients in the NDLS group were not premedicated but the safety results of NDLS were found to be comparable with Taxotere. Conclusion: NDLS formulation with no premedication provides an alternative treatment option for breast cancer patients.

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Introduction

Taxanes are one of the most important cytotoxic agents discovered for the treatment of several types of cancer. Paclitaxel was the first taxane product for which clinical studies indicated an effective response rate and overall survival in breast, lung, ovarian, and gastric cancers.1 However, in some cancers like advanced pancreatic carcinomas, paclitaxel showed lower efficacy compared with docetaxel.2

In metastatic and recurrent head and neck cancer, the combination of paclitaxel and platinum showed lower response compared with docetaxel combination.3 Therefore, in some types of cancers the response rate in patients using paclitaxel treatment might be less compared with patients using docetaxel.

Docetaxel is prepared by semisynthesis beginning with a precursor extracted from the renewable needle biomass of yew plants. It
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is highly lipophilic and practically insoluble in water. Because of its insolubility, the currently marketed docetaxel (Taxotere) is formulated in polysorbate 80 and ethanol and have been approved by the Food and Drug Administration for the treatment of various cancers including locally advanced metastatic breast, non–small-cell lung, and ovarian cancer, and in combination with other drugs for several additional cancer types such as prostate, head and neck, and gastric adenocarcinoma.\textsuperscript{11-17} The use of ethanol and polysorbate 80 in Taxotere formulation causes infusion-related toxicities and hypersensitivity reactions in patients.\textsuperscript{8-10} Thus, the patients are premedicated with corticosteroids to minimize such toxicities before the treatment. To circumvent the toxicities related to polysorbate 80, several investigators developed formulations based on various delivery systems such as liposomes, polymeric micelles, protein, and nanospheres.\textsuperscript{11-17} Nanosomal docetaxel lipid suspension (NDLS) formulation was developed using lipids generally recognized as safe (GRAS) by the Food and Drug Administration and is absolutely free of polysorbate 80 and ethanol. A crossover study conducted at 75 mg/m\textsuperscript{2} with Taxotere in solid tumor patients showed greater systemic availability of docetaxel in patients treated with NDLS compared with Taxotere. In addition, no increase in toxicity was observed compared with Taxotere. The higher systemic availability of NDLS led us to conduct the current efficacy study in breast cancer patients. Results of this study were presented, in part, at the American Society of Clinical Oncology meeting, 2013.\textsuperscript{18} In this study, comparative clinical safety and efficacy of NDLS and Taxotere at 75 mg/m\textsuperscript{2} were evaluated in metastatic breast cancer patients. The improved clinical efficacy of NDLS with no premedication reported here might transform NDLS as a new useful drug for the treatment of cancer.

Patients and Methods

Chemicals and Reagents

Docetaxel was obtained from Scinpharm, Taiwan. NDLS clinical batches were manufactured at a Food and Drug Administration–inspected facility of Intas Pharmaceutical Ltd, India. Soy phosphatidylcholine was procured from Lipoid LLC (Newark, NJ) and sodium cholesteryl sulfate was obtained from Genzyme Pharmaceuticals (Cambridge, MA). Polysorbate-based docetaxel was procured from Aventis Pharma, SA, Paris, France.

Study Design

This was an open label, randomized, multiple dose, parallel study in locally advanced or metastatic breast cancer patients in whom previous chemotherapy had failed. Women, from 18 to 65 years of age, with histopathologically/cytologically confirmed breast cancer, having locally advanced or metastatic breast cancer after failure of previous chemotherapy were enrolled in the study. These patients had Eastern Cooperative Oncology Group (ECOG) performance status \( \leq 2 \), with adequate bone marrow, renal, and hepatic function, having at least 1 measurable lesion according to Response Evaluation Criteria In Solid Tumors (RECIST) 1.1 criteria and also had life expectancy of at least 6 months. The patients were randomized to receive either NDLS or Taxotere.

A total of 72 patients were enrolled into the study at a ratio of 2:1 (NDLS:Taxotere). The mean age of the enrolled patients was 47 years and racial makeup of the study was 100% Asian. Patients were administered NDLS or Taxotere at 75 mg/m\textsuperscript{2} according to the randomization schedule, using intravenous (I.V.) infusion for 1 hour in each cycle of 21 days. Each patient received a maximum of 6 cycles of NDLS or Taxotere. Patients in the NDLS group were not premedicated.

Sexually active women enrolled in the study, unless surgically sterile (at least 6 months before study drug administration) or postmenopausal for at least 12 consecutive months, used an effective method of avoiding pregnancy including oral, transdermal, or implanted contraceptive devices (any hormonal method in conjunction with a secondary method), intrauterine device, female condom with spermicide, diaphragm with spermicide, absolute sexual abstinence, use of condom with spermicide by sexual partner or sterile (at least 6 months before study drug administration) for at least 4 weeks before study drug administration, during study, and up to 30 days after the last dose of study drug. Results of the pregnancy test done at screening were required to be negative.

Treatment and Efficacy Assessments

Each drug, NDLS or Taxotere was administered using I.V. infusion over 1 hour (10-minute deviation was allowed) at a dose of 75 mg/m\textsuperscript{2}. Disease status and tumor response (computed tomography [CT] scan/magnetic resonance imaging) was assessed after every 2 cycles of treatment using RECIST 1.1 guidelines through cycle 6 (including confirmation of response if required); subsequent cycles followed institutional standards for tumor/disease assessment. Independent evaluation (blinded reading) of the images acquired in clinical trial was done at the Central Imaging Facility.

Primary efficacy evaluation was based on the overall response rate (complete response [CR] + partial response [PR]), defined as the proportion of patients whose best overall response was CR (disappearance of all target lesions) or PR after receiving at least 2 cycles of study treatment of NDLS or Taxotere. Patients without a confirmed CR or PR were considered as failure in computing the best overall response rates. The secondary efficacy end point of this study was overall response rate, defined as the proportion of patients in whom disease control rate (CR + PR + stable disease [SD] = disease control rate) from best overall response was CR or PR or SD. Patients without a confirmed CR or PR or SD were considered as failure in computing best overall response rate. The data identified as CR, PR, SD, progressive disease, or not evaluable from independent reviewers was used for the primary and secondary efficacy analysis.

Safety Assessments

Adverse events (AEs) were assessed every cycle for the duration of the trial and graded according to the National Cancer Institute Common Toxicity Criteria, version 4.02. Data on serious AEs were collected throughout the study. Medical history, demography, physical examination and vital signs, body measurement, ECOG, hepatic screening, β-human chorionic gonadotropin test (serum), hematology biochemistry, urine analysis, CT scan, bone scan, echocardiography, and electrocardiogram were carried out as a part of safety and efficacy evaluations.

Statistical Analysis

Primary efficacy analyses are presented for per protocol population who had confirmed CR and PR from the best overall response
and secondary efficacy analysis are presented for per protocol population who had confirmed CR, PR, and SD from the best overall response. A point estimate and a 2-sided 95% confidence interval were computed for the primary efficacy endpoint, response rates (CR + PR) from best overall response of the 2 treatment groups and their difference. A point estimate and a 2-sided 95% confidence interval were computed for the secondary efficacy endpoint, disease control rate (CR + PR + SD) from best overall response of the 2 treatment groups and their difference. An approximate 95% confidence interval (CI) for the proportion is presented. Categorical variables were summarized as counts and percentage. All statistical analysis was performed using SAS Version 9.2 (SAS Institute Inc).

**Conduct of the Study**

Written informed consent was obtained from all patients before enrollment and the study was conducted as per the protocol, International Conference on Harmonization Good Clinical Practice, based on the basic principles of Good Laboratory Practice, Indian Council of Medical Research Guidelines for Biomedical Research on Human subjects, and Declaration of Helsinki (Seoul 2008) on the rights of research participants.

**Results**

**Patient Demographic Characteristics**

A total of 72 locally advanced or metastatic breast cancer patients were enrolled in the study after previous chemotherapy had failed. Baseline demographic and other characteristics between the 2 treatment arms are shown in Table 1.

**Efficacy**

The results of the study were assessed in an independent radiologic review that demonstrated statistically and clinically superior efficacy of NDLS in terms of objective response rates in metastatic breast cancer patients. The NDLS regimen resulted in 35.5% (95% CI, 21.9-48.9%), a higher overall response rate than Taxotere with 26.3% (95% CI, 6.5-46.1%). The disease control rate (CR + PR + SD) was found to be 8% greater for patients receiving Taxotere compared with those who received NDLS. The results are presented in Table 2. It was also observed that 1 patient even showed complete response (disappearance of all target lesions) in the NDLS arm compared with none in the Taxotere arm. Taxotere is approved at a dose range of 60 to 100 mg/m² in the United States and 100 mg/m² in Europe. In the current study, 75 mg/m² dose was selected because of the reports indicating that higher doses are substantially more toxic and are only marginally more effective. In addition, the 100 mg/m² dose is not feasible for some metastatic breast cancer patients heavily pretreated with chemotherapy. Therefore, a dose of 75 mg/m² of NDLS was used in the present study and was found to be effective.

**Safety**

The safety was monitored according to any clinically significant abnormalities (AEs) in treated patients. The post-dose AEs were reported in 91.30% (n = 21) out of 23 patients who received Taxotere and 93.88% (n = 46) AEs were reported out of 49 patients who received NDLS. The NDLS-treated patients were not given any premedication including corticosteroids. In the NDLS and Taxotere treatment groups, 1 or more grade 3 to 4 treatment-related AEs were observed in 77.55% and 52.17% of patients, respectively. The overall increased incidence of neutropenia in NDLS and other AEs were manageable. Most of the post-dose AEs were resolved without any sequelae despite the fact that patients were not premedicated in the NDLS treatment group. Harvey et al. observed that a Taxotere dose of 75 mg/m² in patients with advanced breast cancer who experienced treatment failure with previous chemotherapy resulted in 83.7% neutropenia. Greater AEs were reported at higher dose (100 mg/m²) of Taxotere. Overall, NDLS was found to be tolerable at 75 mg/m² devoid of premedication with corticosteroids (Table 3).

**Discussion**

In the taxane family of cytotoxic drugs, docetaxel is one of the most promising drugs. The polysorbate 80 and ethanol-formulated docetaxel (Taxotere) have been used for the treatment of several types of cancer including breast, head and neck, prostate, non-small lung, and ovarian. Taxotere containing polysorbate 80 also affects the disposition of intravenously administered solubilized drugs and leach plasticizers from polyvinylchloride infusion sets. To minimize the infusion-related toxicities including hypersensitivity reactions, patients are required to receive corticosteroids before administration of the drug. This is due to the occurrence of unpredictable (acute) hypersensitivity reactions and cumulative fluid retention.

Several formulations have been developed including albumin nanoparticles, polyglutamates, taxane analogues and prodrugs,
emulsions, and liposomes, docetaxel—fibrinogen-coated olive oil droplets, docetaxel-encapsulated nanoparticle-aptamer biocojologates, and submicronic dispersion to have an alternative, solvent-free, delivery form for docetaxel. 19-22 Most of these formulations are in the early stages of development and investigators have demonstrated less toxicity and greater efficacy primarily in animal studies. Hennenfent and Govindan 7 reported that preclinical and clinical data from several of these formulations do not have significant advantages compared with Taxotere.

The primary rationale for developing NDLS was to avoid premedication by eliminating polysorbate 80 and ethanol from the commercial Taxotere formulation. In NDLS, docetaxel is formulated with a mixture of well-characterized naturally occurring GRAS lipids. The advantages of using lipids instead of polysorbate and ethanol were several fold. Despite premedication with corticosteroids and histamine antagonists, minor reactions (eg, flushing and rash) still occur in approximately 40% of all patients treated with Taxotere, and nearly 3% of patients still experience potentially life-threatening reactions. 9,22 The exact contribution of polysorbate 80 to antitumor effects has not been understood; however, several reports suggest that it might be linked to the release of oleic acid, a fatty acid known to interfere with malignant cell proliferation, and inhibition of angiogenesis. 7,23,24 It was observed that GRAS lipids were better tolerated than polysorbate 80 and ethanol. Thus, NDLS was administered in patients without the need for premedication with corticosteroids. This also alleviates the danger of leaching plasticizers from infusion bags or tubing.

The pharmaceutical use of lipids have been well documented in several pharmaceutical preparations for oral and i.v. administration. High levels of lipids infused i.v. have also been shown to be safe. 13,14,25 This is consistent with the results reported in the current study in which the NDLS drug appeared to be well tolerated by cancer patients, even as a multiple dose administration. Most of the AEs after dosing were resolved without any sequelae despite the fact that patients were not premedicated.

An earlier pharmacokinetics study revealed that NDLS showed greater systemic availability compared with Taxotere, which potentially could translate into greater efficacy. 18 The current efficacy trial was conducted at equal doses (75 mg/m2) of NDLS or Taxotere and showed an improved efficacy profile with NDLS-treated patients. These findings suggest that the greater exposure of drug using NDLS results in an improved therapeutic outcome in patient populations. Importantly, this trial was conducted in patients in whom previous chemotherapy had failed. The overall response rates observed for Taxotere treatment in our study are similar to those reported by other investigators. 9,22

### Conclusion

Nanosomal docetaxel lipid suspension improves clinical efficacy without any premedication. Thus, it provides a better treatment option for breast cancer patients.

### Clinical Practice Points

- Nanosomal docetaxel lipid suspension is a new formulation developed to overcome toxicity and hypersensitivity reactions caused by excipients (polysorbate 80 and ethanol) of commercially available docetaxel formulations.
- Treatment of breast cancer patients with the improved docetaxel formulation might benefit the patients by shortening the hospital stay required for premedication and resulting in better therapeutic outcome.

### Disclosure

The authors have stated that they have no conflicts of interest.

### References