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Nanosomal Paclitaxel Lipid Suspension Demonstrates Higher Response Rates Compared to Paclitaxel in Patients with Metastatic Breast Cancer

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Abstract

Background/Objective: Nanosomal Paclitaxel Lipid Suspension (NPLS) formulation was developed to eliminate Cremophor EL and ethanol from the currently marketed Paclitaxel (Taxol®) drug for the treatment of cancer patients. The objective of the study was to determine clinical safety and efficacy of NPLS at 80 mg/m^2 and 175 mg/m^2 and compare with Taxol® at 175 mg/m^2 in metastatic breast cancer patients.

Patients and methods: Patients were administered NPLS (n=48, Arm A) or Taxol® (n=27, Arm C) at a dose of 175 mg/m^2 every 3 weeks. Another group of patients were administered with NPLS (n=45, Arm B) at a dose of 80 mg/m^2 every week as per randomization schedule by intravenous infusion. Patients dosed with NPLS were not pre-medicated whereas patients treated with cremophor EL and ethanol based Taxol® were pre-medicated as required. The efficacy was measured by Overall Response Rate (ORR)=Complete Response (CR) + Partial Response (PR) and Disease Control Rate (DCR)=CR + PR + Stable Disease (SD).

Results: (a) Safety- A total of 450 adverse events (AEs) were reported in 97 patients. 157 AEs occurred among patients under NPLS Arm A, 239 AEs occurred to patients under NPLS Arm B and 54 AEs occurred among patients under Arm C. (b) Efficacy- The ORR was 36.4% for NPLS Arm A, 46.5% for NPLS Arm B and 20.8% for Paclitaxel Arm C. The DCR was 86.4% for NPLS Arm A, 88.4% for NPLS Arm B and 83.3% for the Taxol® Arm C.

Conclusion: NPLS produced greater ORR and DCR compared to Taxol® treated patients. The NPLS was tolerated by cancer patients and was found to be an effective anti-tumor agent for breast cancer patients.

Keywords: Paclitaxel; Breast cancer; Efficacy; NPLS

Introduction

Paclitaxel was the first taxane product where clinical studies indicated better response rate and overall survival in breast, lung and ovarian and Kaposi's sarcoma [1-3]. It is highly hydrophobic and practically insoluble in water. Due to its insolubility, the Cremophor EL (CrEL), a polyoxyethylated castor oil vehicle, and dehydrated ethanol USP (1:1, v/v) were used as solvent system in the commercial formulation of paclitaxel (Taxol®). However, the infusion of ethanol and CrEL in Taxol® formulation causes infusion toxicity and hypersensitivity reactions in patients [4-10]. To control these undesirable side effects, the patients are pre-medicated with corticosteroids. In order to circumvent the toxicities related to CrEL and ethanol, several investigators developed paclitaxel formulations using liposomes, polymeric micelles, protein and nanospheres to avoid or minimize the use of solvents [11-19]. In this study, Nanosomal Paclitaxel Lipid Suspension (NPLS) formulation was developed using Generally Recognized as Safe (GRAS) lipid excipients categorized by United States Food and Drug Administration which is free from CrEL and ethanol. A part of this study was presented at the American Society of Clinical Oncology meeting [20].

In this article, comparative clinical safety and efficacy of NPLS (80 mg/m^2, 175 mg/m^2) and Taxol® at 175 mg/m^2 were evaluated in metastatic breast cancer (MBC) patients. This study was designed to assess the feasibility that NPLS without any premedication would be safe and active in patients after failure of prior chemotherapy.

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Materials and Methods

Chemicals and reagents

Paclitaxel was obtained from Bioxel Pharma, Inc. Canada. Soyphosphatidylcholine was procured from Lipoid LLC (Newark, NJ) and sodium cholesteryl sulfate was obtained from Genzyme Pharmaceuticals (Cambridge, MA). Taxol® was procured from Bristol-Myers Squibb, USA.

Nanosomal paclitaxel lipid suspension formulation

The NPLS formulation was prepared using Paclitaxel, Soy Phosphatidylcholine and Sodium Cholesteryl Sulfate in an aqueous medium. In brief, Paclitaxel was added to Soy Phosphatidylcholine and Sodium Cholesteryl Sulfate in an aqueous medium under high pressure homogenization to make less than 100 nm mean particle size of Paclitaxel-lipid suspension. The resulting Paclitaxel-lipid suspension was filled aseptically in vials and subjected to lyophilization. The lyophilized vial was reconstituted with sterile water for injection and further diluted in 5% dextrose Injection. The drug product after dilution was stable up to 8 hour and found to be endotoxin free.

Study design

This was an open label, randomized, multiple dose, parallel study in locally advanced or metastatic breast cancer patients after failure of prior chemotherapy. Females, ≥ 18 years and ≤ 65 years of age, with histopathologically/cytologically confirmed breast cancer, having locally advanced or metastatic breast cancer after failure of prior chemotherapy, having Eastern Cooperative Oncology Group (ECOG) performance status ≤ 2, having adequate bone marrow, renal and hepatic function, having at least one measurable lesion as per the Response Evaluation Criteria In Solid Tumors 1.1 (RECIST 1.1), having life expectancy of at least 6 months were randomized to receive either NPLS or Taxol®.

120 locally advanced or metastatic breast cancer patients in the ratio 2:2:1 (NPLS every three weeks: NPLS weekly: Taxol®) were enrolled into the study after failure of prior chemotherapy. The mean age of the enrolled patients was 48 years and racial make-up of the study was 100% Asian. Patients were administered NPLS or Taxol® at 175 mg/m^2 as per randomization schedule, by IV infusion for 3 hours in each cycle of 21 days in Arm A and Arm C respectively. Each patient received maximum of 6 cycles of NPLS or Taxol®. In Arm B, patients were administered weekly with NPLS at the dose of 80 mg/m^2 for 18 weeks. Patients in the NPLS groups (Arm A and Arm B) were not pre-medicated whereas patients treated with Taxol® were pre-medicated as per the prescribing information.

Patients were excluded if they were having pre-existing motor or sensory neurotoxicity of severity ≥ grade 2 as defined by NCI CTCAE Criteria. Patients previously exposed to Taxane injection, known case of HIV infection and have history of hypersensitivity reactions to drug formulated in Cremophor EL were also excluded. Sexually active women surgically sterile (at least 6 months prior to Study drug administration) or postmenopausal for at least 12 consecutive months or those using effective method of avoiding pregnancy were only enrolled. Results of the pregnancy test in such patients were negative at the time of screening.

Treatment and efficacy assessments

Each drug, NPLS (Arm A, 175 mg/m^2 / Arm B, 80 mg/m^2) or Taxol® (Arm C, 175 mg/m^2) was administered by IV infusion over 3 hours (+ 10 minutes deviation was allowed). Disease status and tumor response (CT Scan/MRI) 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 by Central Imaging Facility.

Primary efficacy evaluation was based on the overall response rate (CR + PR), defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR) after receiving at least two cycles of study treatment of NPLS or Taxol®. Patients without a confirmed CR or PR were considered as failure in computing the overall response rates. The secondary efficacy endpoint was based on the disease control rate (DCR=CR + PR + SD), defined as the proportion of patients whose best overall response was complete response (CR) or partial response (PR) or stable disease (SD). Patients without a confirmed CR or PR or SD were considered as failure in computing disease control rates. The data was analyzed by independent reviewers and used for the primary and secondary efficacy analysis.

Safety assessments

Adverse events were assessed every cycle for the duration of the trial and graded according to the National Cancer Institute Common Toxicity Criteria (NCI CTC), version 4.02. Data on serious adverse events (SAEs) were collected throughout the study. Medical history, demography, Physical examination and vitals, body measurement, ECOG, hepatic screening, β-HCG test (Serum), hematology biochemistry and urine analysis, CT scan, Bone Scan, ECHO and ECG was carried out as a part of safety and efficacy evaluations.

Statistical analysis

Primary efficacy analysis was based on the patients who had confirmed CR or PR whereas; secondary efficacy analysis was based on confirmed cases of CR or PR or SD. A point estimate and a two-sided 95% confidence interval were computed for the primary efficacy endpoint, response rates (CR or PR) from best overall response of the two treatment groups and their difference. A point estimate and a two-sided 95% confidence interval were computed for the secondary efficacy endpoint, disease control rate (CR or PR or SD) from best overall response of the two treatment groups and their difference. All statistical analysis was performed using SAS® Version 9.2 (SAS Institute Inc., USA).

Conduct of the study

Written informed consent was obtained from all patients before enrollment and as outlined in the protocol. International Conference on Harmonization Good Clinical Practice was followed ICMR Guidelines for Biomedical Research on Human subjects, and Declaration of Helsinki (Seoul 2008) on the rights of research participants was also followed for conducting this clinical trial.

Results

Patients demographics

A total of 120 locally advanced or metastatic breast cancer patients were enrolled into the study after failure of prior combination chemotherapy. The prior therapy had included anthracycline unless

Characteristics	NPLS 175 mg/m²	NPLS 80 mg/m²	Taxol® 175 mg/m²	Total
Race				
Asian	48	45	27	120
Age (Years)				
Median	49.0	46.0	46.0	47.5
Range	29-65	26-64	30-64	26-65
Weight (kg)				
Median	49.5	52.0	54.0	51.3
Range	33-83	32-80	33-69	32-83
BSA (/m²)				
Median	1.4	1.5	1.5	1.5
Range	1.2 - 1.8	1.1 - 1.7	1.2 – 1.7	1.1 -1.8
Height (cm)				
Median	152	151	153	152
Range	132-162	134-162	132-164	132-164

*Total number of patients randomized = 120

Table 1: Patient Characteristics and Demographics of patients treated with Nanosomal Paclitaxel Lipid Suspension (NPLS) or Taxol®*.

contraindicated. Demographic data and other characteristics between treatment arms are shown in Table 1.

Safety

A total of 450 adverse events (AEs) reported in 97 patients during the course of the trial. 157 AEs occurred to patients under NPLS Arm A (n=48), 239 AEs occurred to patients under NPLS Arm B (n=45) and 54 AEs occurred to patients under Paclitaxel Arm C (n=27). The NPLS treated patients were not given any pre-medication including corticosteroids. The AEs related to NPLS Arm A, NPLS Arm B and Taxol® Arm C were 68.75%, 68.89% and 48.15% respectively. In both NPLS and Taxol® treatment groups one or more Grade 3 or 4 treatment-related adverse events were observed. The percentage of patients reporting serious Grade 4 AEs in Arm A, Arm B and Arm C were 6.25, 11.11 and 7.41 respectively.

The adverse events occurring after first study treatment are presented in Table 2. The major adverse events observed after the treatment of patients with 175 mg/m² NPLS were Neutropenia (31.25%), Urinary Tract Infections (25%), Alopecia (29.17%), Chills (52.08%) were reported. In Taxol® (175 mg/m²) treated group the major adverse events observed were Alopecia (33.33%), Anemia (18.52%) and Leukopenia (14.81%) whereas, at 80 mg/m² weekly dose of NPLS the major adverse events reported were Neutropenia (44.44%), Anemia (44.44%), Alopecia (33.33%) and Chills (40%). The hypersensitivity was noted in 1 patient and peripheral neuropathy was reported in 3 patients who were receiving NPLS at 80 mg/m². However, none of the patients receiving 175 mg/m² of NPLS every 3 weeks experienced any hypersensitivity and/or peripheral neuropathy. It is to be noted that none of the patients were pre-medicated who received NPLS treatment.

Efficacy

The results of the study were assessed by an independent radiological review board that demonstrated statistically and clinically superior efficacy in terms of overall response rates, in metastatic breast cancer patients. The overall response rate (CR + PR) is 36.4% (95% CI, 22.1- 50.6%) for NPLS treatment-Arm A (175 mg/m²) administered every 3 weeks, 46.5% (95% CI, 31.6- 61.4%) for NPLS treatment-Arm B (80 mg/m²) administered every week and 20.8% (95% CI, 4.6-37.1%) for Taxol® treatment-Arm C (175 mg/m²) administered every 3 weeks. The disease control rates were 86.4%, 88.4% and 83.3% for Arm A, Arm B and Arm C respectively. These results are presented in Table 3. It was observed that 6.8% patients were complete responder in NPLS treatment-Arm A resulting in the disappearance of all target lesions while there was no CR in NPLS treatment-Arm B and Taxol® treatment-Arm C. Further, 29.6% in patients in NPLS treatment-Arm A, 46.5% patients in NPLS treatment-Arm B and 20.8% patients in Taxol® treatment-Arm C had partial response (PR). The imaging data from two patients is presented in Figure 1. The stable disease was found in 50% patients in NPLS treatment-Arm A, 41.9% patients in NPLS treatment-Arm B and 60% patients in Taxol® treatment-Arm C.

Discussion

The current phase II study demonstrated that NPLS, solvent-free lipid formulation of paclitaxel, has an acceptable safety profile and anti-tumor activity in patients with metastatic breast cancer who have failed prior standard chemotherapies.

In NPLS, Paclitaxel is formulated with a mixture of well characterized GRAS lipids. The advantages of using lipids instead of CrEL and ethanol are several folds. Despite premedications with corticosteroids and histamine antagonists, minor reactions (e.g. flushing and rash) still occur in approximately 40% of all patients treated with Taxol®, and nearly 3% of patients still experience potentially life-threatening reactions [9,21]. GRAS lipids appeared to be better tolerated than CrEL and ethanol as excipients. Thus, NPLS was administered in patients without the need of pre-medication with corticosteroids and also alleviates the danger of leaching plasticizers from infusion bags or tubing. In this study, none of the patients receiving 175 mg/m² of NPLS without pre-medication experienced any hypersensitivity and/or peripheral neuropathy.

Adverse Event	NPLS (175 mg/m²) N=48 N (%)	NPLS (80 mg/m²) N=45 N (%)	Taxol® (175 mg/m²) N=27 N (%)
Hematologic			
Neutropenia	15 (31.25)	20 (44.44)	2 (7.41)
Anemia	8 (16.67)	20 (44.44)	5 (18.52)
Leukopenia	6 (12.50)	2 (4.44)	4 (14.81)
Thrombocytopenia	5 (10.42)	1 (2.22)	0
Nonhematologic			
Alopecia	14 (29.17)	15 (33.33)	9 (33.33)
Cough	2 (4.17)	10 (22.22)	2 (7.41)
Diarrhoea	1 (2.08)	4 (8.88)	1 (3.70)
Nausea	2 (4.16)	3 (6.66)	1 (3.70)
Vomiting	3 (6.25)	5 (11.11)	0
UTI	12 (25)	8 (17.78)	3 (11.11)
Peripheral Neuropathy	0	3 (6.66)	0
Pyrexia	7 (14.58)	6 (13.33)	2 (7.41)
Chills	25 (52.08)	18 (40.00)	2 (7.41)

Table 2: Adverse Events Occurring After First Study Treatment of Nanosomal Paclitaxel Lipid Suspension (NPLS) or Taxol®. (ITT, n=120).

Response	NPLS (175 mg/m²) N (%)	NPLS (80 mg/m²) N (%)	Taxol® (175 mg/m²) N (%)
Complete Response	3 (6.8)	0	0
Partial Response	13 (29.6)	20 (46.5)	5 (20.8)
Overall Response Rate	16 (36.4)	20 (46.5)	5 (20.8)
Stable Disease	22 (50)	18 (41.9)	15 (62.5)
Disease Control Rate	38 (86.4)	38 (88.4)	20 (83.3)

* 111 patients qualified for per protocol population for efficacy analysis.

Table 3: Response to Nanosomal Paclitaxel Lipid Suspension (NPLS) or Taxol® (n=111)*.

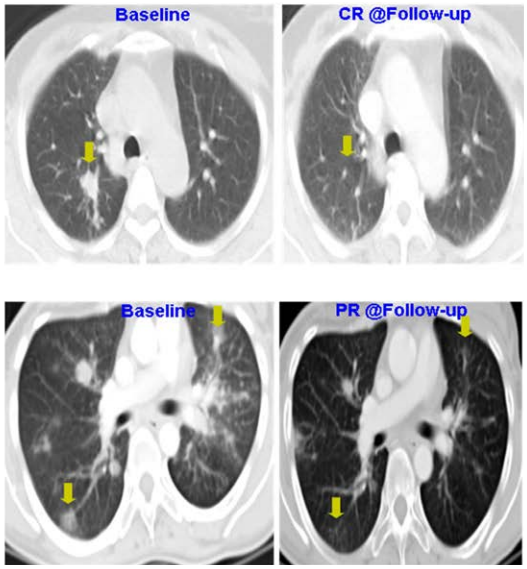

Figure 1: Independent radiologist-assessed Response Rates in patients administered with Nanosomal Paclitaxel Lipid Suspension. Arrow mark indicates complete response and partial response in the lungs of two patients.

The pharmaceutical uses of lipids have been well documented for both oral and intravenous administration. High levels of lipids infused intravenously have been shown to be safe [15,16,25]. In the current study NPLS drug appeared to be tolerated by cancer patients, even as a multiple dose administration. Inspite of the increased incidence of neutropenia, thrombocytopenia, urinary tract infections, pyrexia, chills and other adverse events, the patients treated with NPLS at 175 mg/m^2 majority of the post-dose AEs were resolved without any sequelae despite the fact patients were not pre-medicated.

The current efficacy trial conducted at equal doses (175 mg/m^2) of NPLS or Taxol® showed improved efficacy profile in NPLS treated patients. The weekly dose (80 mg/m^2) of NPLS also showed enhanced response rate in patients. These findings suggest that greater exposure of drug with NPLS results in the improved therapeutic outcome in patient population. Importantly, this trial was conducted in patients who had failed to prior chemotherapy. The overall response rate observed for Taxol® in our study is similar to reported by other investigators [8,21-26].

Conclusion

It is worth pursuing to conduct a larger multi-center trial to further demonstrate NPLS as a new therapeutic option for breast cancer patients. If clinical efficacy results presented in this report are confirmed in large patient population, NPLS without any pre-medication may be a better treatment option for breast cancer patients.

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