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/m2 and 175 mg/m2 and compare with Taxol® at 175 mg/m2 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/m2 every 3 weeks. Another group of patients were administered with NPLS (n=45, Arm B) at a dose of 80 mg/m2 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-mediated 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 practically insoluble in water. Due to its insolubility, the Cremophor EL (CrEL), a polyoxyethylated castor oil vehicle, 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/m2, 175 mg/m2) and Taxol® at 175 mg/m2 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 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/m² 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/m² 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 included. Patients without a confirmed CR or PR were considered as failure in computing disease control rates. The primary efficacy endpoint was based on the disease control rate (DCR=CR + PR + SD), defined as the proportion of patients whose overall response was complete response (CR) or partial response (PR) or stable disease (SD). 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/m² / Arm B, 80 mg/m²) or Taxol® (Arm C, 175 mg/m²) 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 4 weeks 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 (ORR=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®.

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...
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.

**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. 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

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

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

*Total number of patients randomized = 120

**Table 2: Adverse Events Occurring After First Study Treatment of Nanosomal Paclitaxel Lipid Suspension (NPLS) or Taxol®**

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

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

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

<table>
<thead>
<tr>
<th>Response</th>
<th>NPLS (175 mg/m²)</th>
<th>NPLS (80 mg/m²)</th>
<th>Taxol® (175 mg/m²)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Complete Response</td>
<td>3 (6.8)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Partial Response</td>
<td>13 (29.6)</td>
<td>20 (46.5)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Overall Response Rate</td>
<td>16 (36.4)</td>
<td>20 (46.5)</td>
<td>5 (20.8)</td>
</tr>
<tr>
<td>Stable Disease</td>
<td>22 (50)</td>
<td>18 (41.9)</td>
<td>15 (62.5)</td>
</tr>
<tr>
<td>Disease Control Rate</td>
<td>38 (86.4)</td>
<td>38 (86.4)</td>
<td>20 (83.3)</td>
</tr>
</tbody>
</table>

*111 patients qualified for per protocol population for efficacy analysis.
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/m² showed improved efficacy profile in NPLS treated patients. The weekly dose (80 mg/m²) 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.

References

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