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A STUDY ON THERAPEUTIC COMPARISON BETWEEN CONVENTIONAL PACLITAXEL AND NANOPARTICLE ALBUMIN BOUND PACLITAXEL IN BREAST CANCER PATIENTS

Christy Sara Andrews[1]*, Haritha B. Nair[1], Haritha P. Asok[1], Haja Sherief S.[2] and Sivakumar T.[3]

[1]Pharm D Interns, PharmD Department of Pharmacy Practice, Nandha College of Pharmacy, Erode, Tamil Nadu.

[2]M Pharm, Ph D, Head, Department of Pharmacy practice, Nandha College of Pharmacy, Erode, Tamil Nadu.

[3]M Pharm, Ph D, Principal, Nandha College of Pharmacy, Erode, Tamil Nadu.

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***Corresponding Author**
Christy Sara Andrews
Pharm D Interns, PharmD Department of Pharmacy Practice, Nandha College of Pharmacy, Erode, Tamil Nadu.

ABSTRACT

Purpose: The Paclitaxel is proved to be more active in patients who are disease resistant to or who got relapse after the treatment with anthracyclines. The nanoparticle albumin bound paclitaxel (Nab.Paclitaxel) which is free of solvents was compared with polyethylated castor oil based conventional paclitaxel (Con.Paclitaxel) in patients with metastatic breast cancer who were failed in their first line chemotherapy. This study was done to analyse the efficacy and safety of both drugs. **Methods:** A prospective observational study was done at Cancer Centre for 6 months and the sample size was 40 with 20 in each group. Patients were assigned to 4 cycles of either nanoparticle albumin bound paclitaxel intravenously without premedication or conventional paclitaxel intravenously with premedications. **Results and Discussion:** It was found that the overall response rate of Nab.Paclitaxel was higher (65%) when compared with Con.Paclitaxel (35%). Incidence of adverse drug reactions was higher in Con. Paclitaxel than the other group. Among them, grade 4 Neutropenia was high in Con.Paclitaxel group where as Peripheral Neuropathy was found more in Nab.Paclitaxel group. The cost of Nab.Paclitaxel was more than the other group. **Conclusion:** Nab.Paclitaxel was found to be more effective as a second-line treatment for patient with metastasis as the response rate to treatment was higher and the incidence of adverse drug reactions were less

than the other. Though the cost of Nab.Paclitaxel is higher than Con.Paclitaxel, when compared to the benefits of both drugs, Nab.Paclitaxel is found to be the better choice of drug.

KEYWORDS: Breast Cancer, Conventional Paclitaxel, Nanoparticle Albumin Bound Paclitaxel.

INTRODUCTION

Breast cancer is a heterogeneous disease in terms of gene expression, etiology, clinical course and response to treatment.[1,2] According to WHO, among women, breast cancer is the leading cause of death.[3] It occurs when there is uncontrolled growth of breast cells. Such cells continue to grow and form a tumour which can be seen on X-Ray or can be felt as small lumps.[4] Breast cancer occurs mainly in women but in men, it is a rare occurrence with a life time risk of 0.11% compared to about 13% in women.[5] The tumour in the breast can either be benign or malignant.[4] There are many risk factors for breast cancer but it is hard to know how much these factors might have contributed. Being a woman is one of the major risk factors for breast cancer. Age, inherited gene, race and ethnicity and obesity are other main contributors for this disease.[4,5]

The Taxanes have had a great influence in the treatment of variety of cancers like breast cancer, ovarian cancer, non small cell lung cancer and prostate cancer.[6,7] Taxanes when used along with Anthracyclines, they have a significant effect in the treatment.[8,9] Mainly, Paclitaxel and Docetaxel are used to evaluate the efficacy. Paclitaxel was identified as a crude extract from the bark of the North American Pacific yew tree, Taxus Brevifolica in the year 1966 and it is used to treat a variety of cancers.[10-13] The Paclitaxel is proved to be more active in patients who are disease resistant to or who got relapse after the treatment with Anthracyclines.[14] They act by binding with tubulin and stabilize the microtubule bundles which are non-functional, thus leading to subsequent defects in mitotic spindle assembly, chromosome segregation, cell-division and inhibits mitosis, which results in cell death.[2,6,13,15] A dose of 175mg/m^2 over 3 hours every 3 weeks for 4 courses of Paclitaxel is administered as intravenous (IV) after failure of initial chemotherapy for metastatic disease or relapse within 6 months of adjuvant chemotherapy.[16]

Paclitaxel is hydrophobic and thus it requires a complex solvent system to enhance its solubility. A polyoxyethylated castor oil vehicle, cremphor EL ®(CrEL) and dehydrated

ethanol USP are the best option of vehicle system for Paclitaxel.[7,9,13,17-19] In addition, before IV administration the solvent based Paclitaxel must be diluted 5 to 20 fold with 5% dextrose solution.[2,20] As the solvents used in Paclitaxel formulation is pharmacologically and biologically active, they may lead to serious toxicities like hypersensitivity reactions and peripheral neuropathy.[2,12,13,17,21,22] CrEL promotes the release of a plasticizer called di(2-ethylhexyl) phthalate (DEHP) which is released from the standard IV tubing sets that contain Poly Vinyl Chloride (PVC) which subsequently stimulates the release of histamine which results in hypersensitivity reactions including anaphylaxis.[2,7] Thus, to prevent this adverse response, a special infusion set that contains non-poly vinyl chloride tubing with an in line filter must be used with prolonged infusion as well as pre-medications like anti-histamine and corticosteroids and H_2 –blockers are required.[2,7,12,13,18,23,24] Peripheral neuropathy is another major adverse event caused by CrEL. It occurs when CrEL achieves plasma-concentration which will produce axonal swelling, demyelination and axonal degeneration.[12,19,21,25,26] Moreover, CrEL interferes with the efficacy of Paclitaxel and it shows a negative effect to the anti-tumour properties of Paclitaxel. The tumour penetration of the drug is limited due to the formation of CrEL micelles in the plasma compartment results in reduced drug clearance, non-linear pharmacokinetics and free drug fraction.[2,7,12,24] Despite of these premedication, patients will suffer from other adverse reactions like myelosuppression, neutropenia, anaemia, nausea, vomiting and diarrhoea.[16]

Scientists have developed a number of novel taxanes to reduce the potential side effects of Paclitaxel and Docetaxel. One among these new taxanes is Nano Albumin Bound paclitaxel (Nab.Paclitaxel).[2,19,27,28] Nanoparticles are usually composed of non-toxic, biodegradable lipid based and polymeric materials which under certain conditions allow the addition of tumour-targeting molecules. They have the capacity to carry large loads molecules and thus can easily undergo degradation.[29,30] An effective anti-cancer drug will be able to reach the desired tumour tissues through minimal loss of the activity in blood circulation. Also, the drugs after reaching the tumour tissue will have the ability to selectively kill the tumour cells without affecting the normal cells. Nanoparticles can satisfy these requirements which make them more effective drug carrier systems.[31]

Nab. Paclitaxel is a novel development which is a first generation nanoparticle, in which a serum albumin is included as a carrier.[14,31-32] The Nab.Paclitaxel formulation has an improved response rate in breast cancer and it is proved to be very effective in treating

metastatic lesions.[29,32] Abraxane; American Bioscience Inc, Santa Monica, California(ABI-007) is the first protein stabilized, biologically interactive, Nanometre Sized Albumin Bound Paclitaxel which was approved by Food and Drug Administration in 2005.[12,14,28,33-36] Nab.Paclitaxel is a hydrophobic, solvent-free colloidal suspension of nanoparticles of size 130- 150nm which is prepared by high pressure homogenisation of Paclitaxel in the presence of serum albumin (3-4%).[12,19,22,28] The formulation of Nab.Paclitaxel has several advantages over classical formulation of Paclitaxel such as no requirement of premedications, lesser intravenous infusion time(30 minutes vs. 3 hours), no special infusion set required, it can be administered at higher dose and has lesser side effects.[9,12,14,19,28,37]

Albumin acts as a carrier that binds to Glycoprotein 60 (gp60) receptor activates caveolin-1. This results in the formation of caveoli that transports albumin across the endothelial cells to the interstitial space. Similarly, secreted protein, acidic and rich in cysteine (SPARC) which is a matricellular protein also contributes to higher intra tumoral concentration of Nab.Paclitaxel. Thus, Nab.Paclitaxel increases its tumour targeting through 2 ways: gp60 receptor caveolae mediated endothelial transcytosis and in connection with the albumin bound protein SPARC in the tumour microenvironment so that it can achieve enhanced intratumoural concentrations.[2,19] Metastatic breast cancer patients are given a dose of 260mg/m^2 administered as IV infusion over 30 minutes every 3 weeks. The Nab.Paclitaxel is reconstituted aseptically by injecting 20ml of saline.[35]

MATERIALS AND METHODS

A prospective observational study on the therapeutic effects, safety and prevention of drug related problems by using therapeutic and pharmaceutical means of Con.Paclitaxel and Nab.Paclitaxel was done at a Cancer Centre. Protocol and related materials were approved by the Institutional Ethics Committee. Written Informed consent was taken from all patients.

Patients

A total of 43 patients were enrolled in our study and among them 3 were withdrawn due to their personal reasons. They were divided into two groups comprising of 20 in each. Non-pregnant, non-lactating women of age 18 – 70 who received Con.Pacltaxel and Nab.Paclitaxel were selected. Those who were failed in the first line chemotherapy, with an Eastern Coperation Oncology Group (ECOG) performance status on 0- 2 and who had life expectancy of atleast 3 months were chosen for this study.

Treatment

Con.Paclitaxel was administered as a continuous intravenous infusion over 3 hours every 3 weeks for 4 cycles, patients received corticosteroids (dexamethasone) and antihistamines (diphenhydramine) as pre - medications. On the other hand, Nab.Paclitaxel was given as a continuous intravenous infusion over 30 minutes every 3 weeks and the patients did not receive any medications prior to the treatment.

Response and Toxicity Criteria

Computed Tomography (CT) scan was performed at baseline and after 4 cycles of therapy to assess the radiological response of each patient. It was analysed by using Response Evaluation Criteria In Solid Tumors (RECIST) criteria version 1.1. The Clinical Benefit Ratio (CBR), which is the percentage of patients who had a Complete Response (CR), Partial Response (PR) or stable disease, was also checked. Adverse drug reactions (ADRs) of both drugs were analyzed by scale and reported. Neutropenia was measured using Common Toxicity Criteria (CTC) version 2.0 and peripheral neuropathy was assessed using ECOG grading scale for Chemotherapy Induced Peripheral Neuropathy (CIPN).

RESULTS

Patient Population

In this study, all patients were female of age 18- 70. They were divided into four groups according to their age. Among them most of the patients were in the age group of 51-60. The subjects in this study have already failed in the first line treatment with anthracycline and most of them have used FAC (Fluorouracil, Doxorubicin and Cyclophosphamide) in their adjuvant setting. A total of 21 patients exhibited post operative recurrence from both groups. The patients who underwent chemotherapy with these drugs have tumour metastasis to various sites. Among them, the metastatic sites were the lymph nodes in 27 patients, liver in 12, lungs in 18, bones in 6, kidney and gallbladder in one each. A total of 13 patients had metastasis to multiple organs. The physical status of the patients were assessed before enrolling them for our study. It was done according to the ECOG performance scale. As per our inclusion criteria, patients with ECOG performance of ≤ 2 were only selected for our study. In both the cases, most of the patients were included in physically restricted state. For those who were in Con.Paclitaxel group, a dose of 260 mg/m^2 was administered whereas individualised dosing was performed in patients who received Nab.Paclitaxel according to the

Body Surface Area (BSA) using Dubois formula. None of the patients in Nab.Paclitaxel group received any pre-medications.

Efficacy

Among 20 patients who received Nab.Paclitaxel, 40% (8 patients) showed partial response to the treatment whereas only 20% (4 patients) responded partially to Con.Paclitaxel. In our study, complete response to the treatment was significantly greater for Nab.Paclitaxel than for Con.Paclitaxel (25% versus 15%) respectively. However, in CT scan majority of the patients (40%) who took Con.Paclitaxel didn't showed any shrinkage in the size of tumour whereas only 20% showed stable condition in the case of Nab.Paclitaxel. The disease was progressed in 5 patients in the Con.Paclitaxel group.(Fig 1) The overall response rate (CR+PR) of Nab.Paclitaxel is higher (65%) when compared with Con.Paclitaxel (35%).

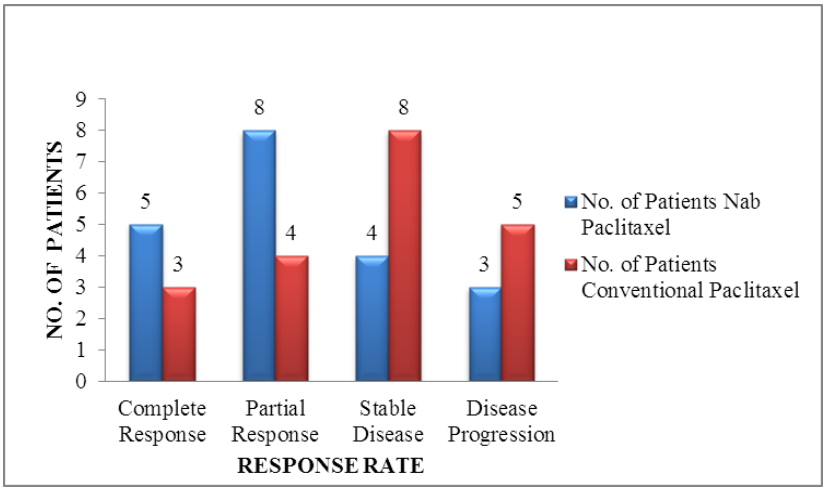

Fig. 1: Comparison of Response Rate of Nab-Paclitaxel and Conventional Paclitaxel Patients.

Safety

All 40 patients were included in the safety analysis and most of them received a specific dose. As per protocol, corticosteroids and anti histamines were not administered to those taking Nab. Paclitaxel whereas all patients in Con.Paclitaxel group received premedication in all the cycles. Most of the cytotoxic reactions were observed in the patients and among them peripheral neuropathy and neutropenia were of greater concern. The other most common Adverse Drug Reactions (ADRs) that occurred in Nab.Paclitaxel when compared with Con.Paclitaxel are nausea (90% versus 65%), vomiting (55% versus 35%). On the other hand, leukopenia (55% versus 30%), lymphopenia (50% versus 30%), rashes (50% versus

35%), anaemia(40% versus 15%), loss of weight (65% versus 50%), thrombocytopenia(45% versus 30%), diarrhoea (50% versus 20%), loss of appetite (80% versus 50%) were seen more in Con.Paclitaxel than the other, occurrence of alopecia was there in all 40 patients whereas ADRs like constipation and thrombocytosis were observed only in Nab.Paclitaxel group and that was with a percentage of 30% and 10% respectively.(Table 1).

Table. 1: Adr Occured in Patients Taking Conventional Paclitaxel.

Adverse drug reactions	Con. Paclitaxel group	Nab. Paclitaxel group
Neutropenia	8	13
Peripheral neuropathy	15	9
Leukopenia	6	11
Lymphopenia	6	10
Nausea	18	13
Vomiting	11	7
Diarrhea	4	10
Alopecia	20	20
Constipation	6	0
Thrombocytopenia	6	9
Thrombocytosis	2	0
Anaemia	3	8
Low	10	13
Loa	10	16
Insomnia	11	16
Rash	7	10

And Nab Paclitaxel

In our study, grade 4 neutropenia was found in 4 patients who took Con.Paclitaxel but it was only in 2 patients in Nab.Paclitaxel (20% versus 10%). Similarly, grade 3 neutropenia has occurred only in 4 patients of Nab.Paclitaxel when compared with 5 patients who received Con.Paclitaxel(20% versus 25%).(Fig 2) Altogether neutropenia was found more in Con.Paclitaxel group. Peripheral neuropathy is another key adverse response in patients who were treated with Paclitaxel. The incidence of a severe form grade 3 of this effect was greater in the Nab.Paclitaxel group than the Con.Paclitaxel group (40% versus 15%). Incidence of grade 4 peripheral neuropathy was absent in both cases. Also, the overall incidence of this event was higher in Nab.Paclitaxel. (Fig 3).

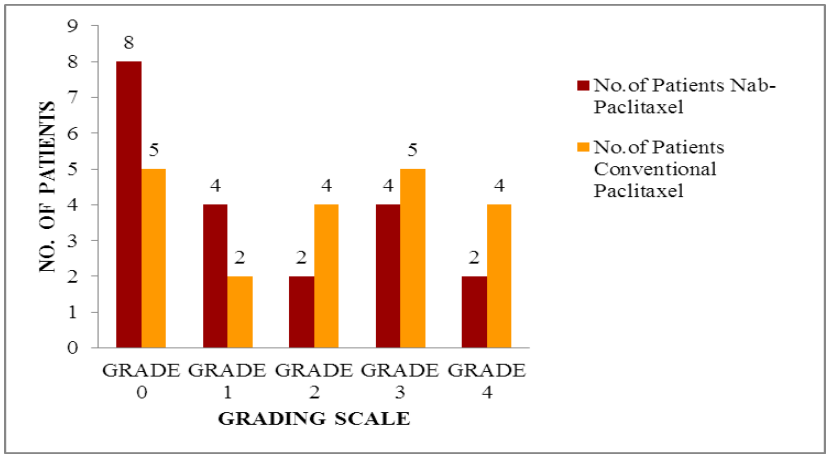

Fig. 2: Comparison of Neutropenia in Nab- Paclitaxel And Conventional Paclitaxel.

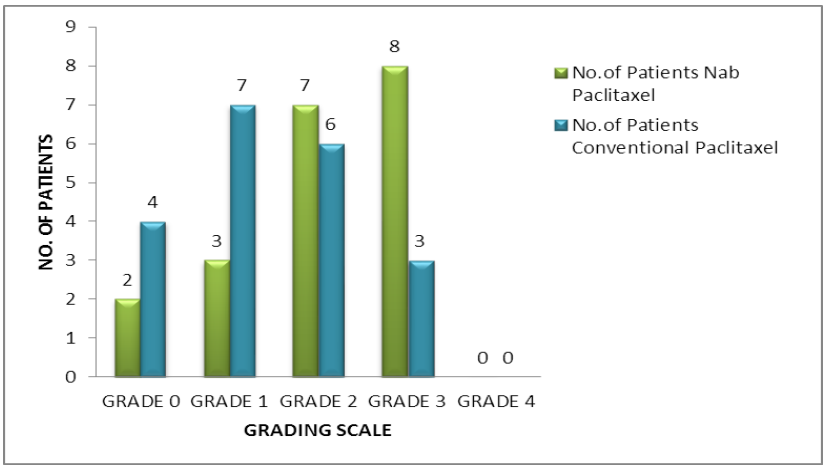

Fig. 3: Comparison of Peripheral Neuropathy in Nab -Paclitaxel and Conventional Paclitaxel.

No treatment death occurred in both groups throughout the study time. Counter measures for the adverse reactions were given to the patients for better tolerability of the drugs. Dose reduction was not performed in any of the subjects. We provided the patients with drug management counselling prior to the treatment. Information regarding the drug, its goal, treatment schedules, potential adverse events and its counter measures were given to the patients.

DISCUSSION

In this study, Nab.Paclitaxel was found to be superior to Con. Paclitaxel in patients with metastatic breast cancer. The efficacy was evaluated after considering the CT scan which was taken at the baseline and after 4 cycles of treatment. The tumour response for target lesions after 4 cycles of chemotherapy is considered and the response can be complete, partial, stable

or progression. The complete as well as partial response showed by patients to Nab.Paclitaxel was significantly higher than the other. On the other hand, stable disease condition and progression of disease was found more in case of Con.Paclitaxel. Similarly the overall response rate was also high for Nab.Paclitaxel. The Clinical Benefit Ratio (CBR) which is defined as the percentage of patients who had a Complete Response (CR), Partial Response (PR) and stable disease. In the study, it was found that the CBR was higher for Nab.Paclitaxel than Con.Paclitaxel (85% versus 75%). Gradisher *et al.*, pointed out that the anti-tumour activity and intratumour Paclitaxel concentration was higher for Nab.Paclitaxel when compared with Con.Paclitaxel.[14] In the same way, the response rate and CBR were markedly higher in patients with metastasis to a single organ than in those with metastasis to multiple organs.

The safety profiles of both the groups were compared and almost all the patients experienced mild to moderate ADRs. We monitored Blood Pressure, Pulse Rate and Heart Rate of the patients before, during and after the administration of both the drugs. In this study, the severe form of neutropenia was found more in Con.Paclitaxel than in Nab.Paclitaxel. The grade 3 neutropenia was also high in case of Con.Paclitaxel. A study by Kosei Kimura *et al.*, stated that the occurrence of grade 4 neutropenia was lower for Nab.Paclitaxel compared with Con. Paclitaxel. Similarly, the incidence of grade 4 neutropenia was significantly less in Nab.Paclitaxel with that of Con.Paclitaxel.[38]

Another main adverse response in patients who were treated with paclitaxel is peripheral neuropathy. No severe form of this was occurred in any of the patients of both groups. But grade 3 peripheral neuropathy was greater in Nab.Paclitaxel when compared with the other. The overall incidence of this event was also higher in case of Nab.Paclitaxel. In a study conducted by H.S.Rugo *et al.*, reported no grade 4 neuropathy and it was stated that incidence of grade ≥2 neuropathy was increased with Nab.Paclitaxel compared with Con.Paclitaxel.[39] In our study, the episode of grade ≥2 peripheral neuropathy was greater in Nab.Paclitaxel than in Con.Paclitaxel group. Other ADRs like nausea and vomiting were high in Nab.Paclitaxel group but rashes, lymphopenia, leukopenia, diarrhoea, loss of weight were more in Con.Paclitaxel group. Alopecia has occurred in all patients in this study.

The hypersensitivity reactions can occur after the administration of Con. Paclitaxel drugs. The hypersensitivity reactions occur due to the polyoxyethylated castor oil, Cremphor EL (CrEL) that is present in drug. The chances of such reactions were higher in Con.Paclitaxel,

so they received pre-medications with Corticosteroids and Anti-Histamines to avoid them. No severe hypersensitivity reactions occurred with Nab.Paclitaxel despite the absence of pre-medication and shorter administration time.

Counter measures for the adverse reactions were given to the patients for better tolerability of the drugs. In case of neutropenia, subcutaneous injection of Granulocyte Colony-Stimulating Factor (G-CSF) and treatment with anti-bacterial agents are required for patients who had grade ≥3 neutropenia. In our study, 13 patients with Con.Paclitaxel and 8 patients with Nab.Paclitaxel were administered with Filgrastim 300 mcg due to severe neutropenia. There was occurrence of mild to moderate infections in patients with higher degree of neutropenia and such patients were administered with antibiotics like Ciprofloxacin 500mg every 12 hours.

Another major adverse event of these drugs is peripheral neuropathy and in such patients, the measures like symptomatic treatment with drugs were administered as required. Supportive medical therapy by using analgesics and vitamins were given for patients with peripheral neuropathy. These agents were shown to be effective in managing neuropathy in patients of both groups. In one patient, the occurrence of this event was severe and that patient was given Glutamine, which is an amino acid. The symptoms resolved completely within 6 days after the intake of the drug.

Dose reduction was not performed in any of the subjects. In a study conducted by Argyriou A A *et al.*, it was said that Vitamin E can be used as anaphylaxis against chemotherapy induced neuropathy.[40] Also, Kumar Gaurav *et al.*, stated that glutamine improves the neurologic toxicities that can occur due to cancer chemotherapy.[41] In the same way, in our study glutamine, vitamin and analgesics like Diclofenac were proved to be effective in reducing the neurologic pain. Anti-emetics were given to treat nausea and vomiting. Other reactions occurred were in mild frequency, therefore prophylactic treatment for them were administered only when it is required.

The supportive care was given to the patients who underwent our study. As the breast cancer therapy produces a number of adverse effects which directly influence the quality of life, it is important to reduce the anxiety in patient. In the same way, communication with patients was essential in the detection of the adverse events. Therefore, we provided the patients with drug management counselling prior to the treatment. Information regarding the drug, its goal,

treatment schedules, potential adverse events and its counter measures were given to the patient. Also, pamphlets were given to the patient regarding breast cancer, its non-pharmacological treatment and the diet that should be followed by cancer patients.

During one infusion, the whole infusion stopped by 25 minutes instead of 30 minutes. This happened due to improper validation of infusion set. The patient was found to be safe and no clinical changes observed in the condition of the patient.

The pharmacoeconomic study for both the drugs was done in all the patients. When treatments are not equal in terms of efficacy or outcome, a cost utility analysis was undertaken. It was found in our study that Nab.Paclitaxel is more expensive than Con.Paclitaxel as each vial of Nab.Paclitaxel costs more when compared with the latter. More vials are required in case of Nab.Paclitaxel as the dose is calculated according to BSA. Therefore, though Nab.Paclitaxel is costlier than Con.Paclitaxel, its improved efficacy, reduced adverse effect and more convenient administration may offset the increased expense of the drug. It was similar to the findings of Thomas E Stinchcombe *et al*.

CONCLUSION

Our study concluded that Nab.Paclitaxel has more advantages when compared to Con.Paclitaxel in terms of efficacy and safety. Nab.Paclitaxel was found to be more effective as a second-line treatment for patients with metastasis as the response rate to treatment was higher in Nab.Paclitaxel when compared to patients who took Con.Paclitaxel. It also allowed infusion of higher dose of drug within shorter duration and without any pre-medications.

Nab.Paclitaxel showed better tolerability compared to Con.Paclitaxel with lower incidence of ADRs. The chance for the occurrence of hyper sensitivity reactions were less as the usage of pre-medications were absent in them. Though, the cost of Nab.Paclitaxel is higher than Con.Paclitaxel, when compared to the benefits of both drugs, Nab.Paclitaxel was found to be the better choice of drug.

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CONFLICT OF INTEREST

The author declares there is no conflict of interest.

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