Original Article

Oncology Section

A Comparative Analysis on the Efficacy and Safety of Intaxel® and Taxol® in Advanced Metastatic Breast Cancer

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ABSTRACT

Background: Among the presently available cytotoxic drugs, paclitaxel, in combination with doxorubicin and carboplatin, come under the highly active therapy for metastatic breast cancer. Between the two brands of paclitaxel (Intaxel, which is marketed by Fresenius Kabi and Taxol, the original paclitaxel which is manufactured by BMS) the similarity has not been evaluated in clinical trial settings till date. This prospective, controlled, randomized, multicentre, open-label phase IV study was planned to compare the safety and efficacy of Intaxel with Taxol, when they were used in combination with carboplatin or doxorubicin, as a second line treatment for metastatic breast cancer.

Methods: Fourty nine eligible patients were randomized to receive Intaxel or Taxol with either doxorubicin or carboplatin. The patients who had received a prior anthracycline based chemotherapy were randomized to the paclitaxel/carboplatin arm. The patients were evaluated in three phases i.e. at baseline, during the treatment and at follow up for the tumour response, the time period till the disease progression and the toxicity. The time till the disease progression was assessed by the Kaplan–Meier method. The continuous and categorical variables were assessed by using the ANOVA test and Fisher's exact test, respectively.

Results: After 3 cycles, an objective response rate of 55.56% (CR = 3, PR = 7) was noted in the Intaxel group and that of 59.09% (CR = 1, PR = 12) was noted in the Taxol group. After 6 cycles, an objective response rate of 50% was noted in both the groups. No significant difference was observed in the response rate of the two groups after 3 cycles ($p > 0.05$) and at the end of the treatment ($p > 0.05$). The patients who received Intaxel had a lower incidence of thrombocytopaenia ($p = 0.0146$) and neurosensory loss ($p = 0.008$) as compared to those who received Taxol.

Conclusion: The results of this study demonstrated that the safety and efficacy of Intaxel and Taxol are equivalent when they are used in combination with other cytotoxic agents as the second line of treatment for metastatic stage IV breast cancer.

Key Words: Intaxel, Taxol, Paclitaxel, Metastatic breast cancer

INTRODUCTION

Breast cancer is one of the most common malignancies which affect women all over the world [1-2]. The use of systemic chemotherapy in metastatic breast cancer improves the quality of life and it delays the disease progression; however, the aim remains largely palliative. Among the presently available chemotherapy options; paclitaxel, doxorubicin and carboplatin are highly active [3-4].

Paclitaxel was introduced in the 1990s and since then, it has been a major focus of the active clinical and laboratory research for its optimal integration into new treatment strategies for patients with breast cancer [5-6]. With the emergence of the taxanes as one of the most effective classes of treatment for breast cancer, clinical trials were conducted to determine the efficacy and the safety of the anthracycline/taxane combinations [7-9]. Doxorubicin or carboplatin, combined with paclitaxel, have shown good efficacy in the previously treated patients with metastatic breast cancer [1, 10-11]. The available data and experiences with the paclitaxel-based therapy in patients with advanced breast cancer indicate that the treatment may cause regression of the tumour and also delay the time till the disease progression [10-15].

The US-FDA has approved paclitaxel (Taxol, Bristol-Myers Squibb Company; Princeton, NJ) as a second line therapy for advanced metastatic breast cancer. The Dabur Research Foundation (DRF) has also introduced the paclitaxel which can be retrieved from the leaves of the Himalayan yew tree by using an environment friendly manufacturing technique without harming the tree itself. The marketing authorization of Fresenius Kabi's brand of paclitaxel, "Intaxel", was granted by The Drug Controller General of India in the year 1994. Subsequent to this, Intaxel has been launched successfully in many global markets for the same indications as Taxol.

So far, the equivalence of these two brands has not been evaluated in clinical trial settings. This study evaluated the safety and efficacy of Intaxel in comparison to those of Taxol. The primary objective of this study was to compare the toxicity and efficacy of Intaxel with those of Taxol®; when they were administered in combination with either doxorubicin or carboplatin, as a second line option in patients with advanced metastatic breast cancer.

METHODS

Study Design

This was a prospective, randomized, active-controlled, multicentre, open-label phase IV parallel group study. This study was approved by the Central Ethical Committee and informed written consents were obtained from all the patients prior to their enrollment. All the

eligible patients were randomized to receive Intaxel or Taxol with either doxorubicin or carboplatin. The patients who had received a prior anthracycline based chemotherapy were randomized to the paclitaxel/carboplatin arm.

Patients

From Apr-2001 to Feb-2003, women with histologically confirmed metastatic breast cancer and measurable disease entered this study. The patients were declared as eligible if they had received a prior treatment with or without anthracyclines. However, the patients who received prior paclitaxel were not considered to be eligible. Only those patients with the following specifications were included in the study: adequate bone marrow and renal, cardiac or liver functions which were as follows: WBC > 3000 /mm3, ANC > 2000/mm3, Platelets > 75,000 /mm3, Hb > 10 g/dl; serum biochemistry levels: AST, ALT < 2.5 x upper limit of normal range (ULN); Total bilirubin < 1.5 times, ULN Serum Creatinine < 1.5 times, ULN Calcium < 10.5 mg/dl; measured or evaluated urinary creatinine clearance > 60 ml/min; no signs of respiratory insufficiency; a stable cardiac status and heart rhythm and no clinical evidence of congestive heart failure or conduction abnormalities. The patients were required to have an Eastern Co-operative Oncology Group (ECOG) Performance status of 0-2. The patients with metastatic Central Nervous System (CNS) disease were excluded.

Treatment Plan

Doxorubicin was administered at a dose of 60 mg/m2 (in 100 ml normal saline as a 30 min infusion) on day 1, followed by paclitaxel as a 3 hr continuous iv. infusion in 500 ml of normal saline at a dose of 175 mg/m2, cyclically on day 1 or 2, every 3 weeks for six cycles. The patients who were on carboplatin received paclitaxel as a 3 hour continuous iv. infusion in 500 ml of normal saline at a dose of 175 mg/m2 on Day 1, once every 3 weeks, followed by carboplatin (Area under the Curve; AUC = 4-5, Calvert formula) on day 2 in 5% Dextrose, 250 ml over 30 min, cyclically every 3 weeks for six cycles. The patients were pre-medicated for paclitaxel as per the established regimen.

The Toxicity and Response Assessments

The tumour response was assessed at the end of the third and six cycles by X-ray, computed tomography scans, magnetic resonance imaging, or clinical examinations according to the WHO criteria. The toxicity was evaluated according to the NCI-CTC version 2.0 criteria.

STATISTICAL ANALYSIS

The time till the disease progression was calculated from the date of enrollment of the women in the study to the date of disease progression and it was assessed by the Kaplan–Meier method. Statistical analyses were performed by using Fisher's exact test and the ANOVA test. All the tests were two-sided with a 95% significance level. The statistical analysis was performed by using SAS Proc Mixed, Version 8.2.

RESULTS

A total of 49 subjects were enrolled in the study and they were randomized to four treatment arms as follows: Group 1a: Intaxel+doxorubicin (n=4); Group 1b: Intaxel+carboplatin (n=21); Group 2a: Taxol+doxorubicin (n=4); and Group 2b: Taxol+carboplatin (n=20). Forty two patients completed 3 cycles, but 2 patients were excluded from the analysis, since their radiological data was unavailable and hence, 40 patients were assessed for the efficacy of the treatment. Out of the 31 patients who completed 6 cycles, 30 were evaluated for the response to the treatment due to the unavailability of the data of one patient. All the 49 subjects who were enrolled were evaluated for the toxicity end points.

The baseline patient characteristics were similar between the two paclitaxel study groups. The median age of the patients was 58.3 ± 9.5 years (range- 27-69 years). Post-menopausal patients constituted approximately 92% (n= 45) of the patients who were enrolled. The ECOG status and the patients who completed the treatment cycles have been presented in [Table/Fig-1].

Efficacy Results

The response to the treatment was evaluated in 40 patients (18 in the Intaxel group and 22 in the Taxol group) who completed a minimum of 3 cycles of chemotherapy, and in 30 patients (14 in the Intaxel group and 16 in the Taxol group) who completed 6 treatment cycles.

After 3 cycles, objective total response rates of 55.6% and 59.1% were noted in the Intaxel and the Taxol groups, respectively. At the end of 6 cycles, the total response rate was found to be similar (50%) in both the groups. There was no difference in the response rates of the two groups (p>0.05) at the end of 3 and 6 cycles. The response rates have been summarized in [Table/Fig-2].

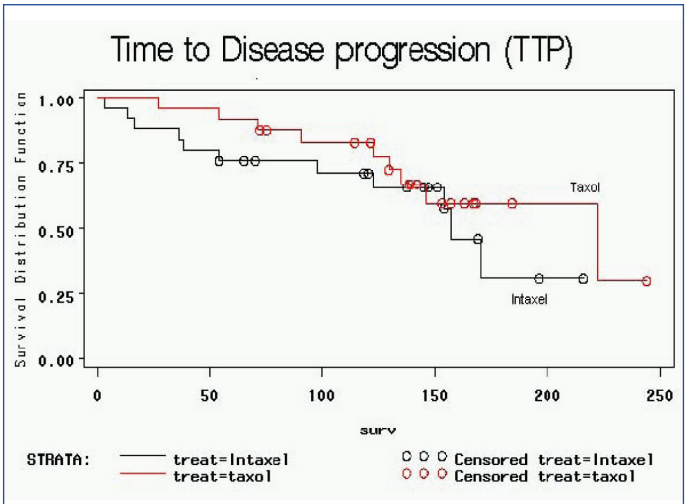
As shown in [Table/Fig-3] and [Table/Fig-4], the disease progression rate was alike between both the treatment groups. The number of patients with disease progression were 11 (44%) vs. 9 (37.5%) in the Intaxel and the Taxol groups respectively. The median time till the disease progression (TTP) for Intaxel was 157 days as compared to 222 days in the Taxol group. However, the difference was not statistically significant (log rank p=0.3607).

	Intaxel (Group 1; n = 25)	Taxol (Group 2; n = 24)
ECOG Grade		
Grade 0	13	15
Grade 1	10	9
Grade 2	2	0
Patients completing number of treatment cycles		
3 cycles	19	23
6 cycles	15	16

[Table/Fig-1]: ECOG status and Treatment cycles in study population

	Intaxel (Group 1)	Taxol (Group 2)
Number of subjects with evaluable 3 cycles	18	22
Complete Response (CR)	3	1
Partial Response (PR)	7	12
Incomplete Response (IR)	6	6
Progressive Disease (PD)	2	3
Number of subjects with evaluable 6 cycles	14	16
Complete Response (CR)	3	2
Partial Response (PR)	4	6
Incomplete Response (IR)	4	5
Progressive Disease (PD)	3	3

[Table/Fig-2]: Response evaluation after three and six cycles of chemotherapy



[Table/Fig-3]: Kaplan-Meier graph showing disease progression rate

Safety Results

All the patients who received at least one dose of treatment were included in the safety data analysis. Overall, the treatment was well tolerated. Only one incidence of hypersensitivity was reported

	Intaxel	Taxol
Number Randomized	25	24
No. of subjects with Disease Progression	11	9
No. of subjects without Disease Progression (censored)	14 (56%)	15(63%)
Median TTP (days)	157	222
95% Lower Confidence Interval TTP (days)	122	134
Hazard Ratio (95% Confidence Limits)	1.525 (0.612, 3.797)	
Log-Rank p-values	0.3607	

[Table/Fig-4]: Time to Disease Progression (TTP)

	Intaxel Group					Taxol Group				
	CTC Grade					CTC Grade				
Adverse event	Grade 1	Grade 2	Grade 3	Grade 4	Total	Grade 1	Grade 2	Grade 3	Grade 4	Total
Alopecia	2	8	2	3	15 (60%)	1	17	1	2	21 (88%)
Asthenia	2	4			6 (24%)	8	3			11 (46%)
Neurosensory loss		1			1 (4%)	5	3			8 (33%)
Nausea	5				5 (20%)	3	3			6 (25%)
Vomiting		1	1		2 (8%)		3			3 (13%)
Myalgia	1				1 (4%)	2	3			5 (21%)
Pain in limbs	1	1			2 (8%)	1	1			2 (8%)
Diarrhoea	1	1	1		3 (12%)	1				1 (4%)
Cough		1			1 (4%)		1			1 (4%)
Fever					-	3				3 (13%)
Loss of appetite					-	2	1			3 (13%)
Headache					-		2			2 (8%)
Abdominal pain					-	1	1			2 (8%)
Motor Neuropathy					-		1			1 (4%)
Nail changes					-	1				1 (4%)
Hypersensitivity					-		1			1 (4%)
Urticaria					-	1				1 (4%)
Skin hyperemia					-		1			1 (4%)
Flushing	1				1 (4%)					-
Nail pain	1				1 (4%)					-
Bone pain	1				1 (4%)					-
Tachycardia	1				1 (4%)					-
Epistaxis	1				1 (4%)					-
Epigastric pain		1			1 (4%)					-
Somnolence		1			1 (4%)					-
Conjunctivitis					-	1				1 (4%)
Superficial phlebitis					-		1			1 (4%)
Lymphedema					-		1			1 (4%)
Aphthous ulcer					-		1			1 (4%)
Sacral abscess					-		1			1 (4%)
Loss of consciousness					-		1			1 (4%)

[Table/Fig-5]: Percentage data of non-hematological adverse events

Adverse event	Intaxel Group					TaxolGroup				
	CTC Grade					CTC Grade				
	Grade 1	Grade 2	Grade 3	Grade 4	Total N (%)	Grade 1	Grade 2	Grade 3	Grade 4	Total N (%)
Leukopenia	2	5	9	2	18 (72)	3	9	9	1	22 (92)
Anemia	4	6	3	2	15 (60)	2	4	5	-	11 (46)
Thrombocytopenia	3	1	4	1	9 (36)	11	3	2	1	17 (71)
Neutropenia	5	2	7	4	18 (72)	-	7	4	7	18 (75)
Lymphocytopenia	1	2	-	-	3 (12)	2	-	-	-	2 (8)
Hematocrit	-	1	-	1	2 (8)	1	-	-	-	1 (4)

[Table/Fig-6]: Incidence of hematological Toxicities as per CTC Criteria

during the study. [Table/Fig-5 and 6] represent the reported non-haematological and haematological adverse events. A significant lower incidence of neurosensory loss was observed in the Intaxel group (1/25 vs. 8/24, p = 0.008 for Intaxel vs. Taxol). Similarly, a lower incidence of thrombocytopaenia was observed in the Intaxel group (9/25) as compared to that in the Taxol group (17/24) (p = 0.0146). Other reported toxicities were comparable in both the groups.

Five patients in the Intaxel group and three in the Taxol group discontinued their treatments due to adverse events. One death was reported during the study, which was not related to the treatment. This patient was diagnosed with brain metastasis, 3 days after the first cycle of the therapy.

DISCUSSION

The introduction of paclitaxel for the treatment of breast cancer led to an improvement in the management of advance diseases. The inclusion of paclitaxel as a part of the combination chemotherapy for metastatic breast cancer has evolved as a standard care, especially, due to the good response rate and the increased time to progression [15-16].

Our study provides evidence that the use of Intaxel in combination with docetaxel or carpolatin as a second line treatment regimen gives equivalent overall survival advantages to the regimen, which includes Taxol. Both Intaxel and Taxol demonstrated comparative response rates after 3 and 6 cycles ($p > 0.05$) The average response rate which was achieved in our study patients was 50%-60%. In various clinical trials, paclitaxel, in combination with carboplatin or doxorubicin for metastatic breast cancer, showed similar response rates [11,17-19]. Similar response rates were observed with the paclitaxel therapy in metastatic breast cancer patients with and without a prior exposure to anthracyclines [14].

The TTP rate and the hazard ratio were similar between both the treatment groups, thus indicating that Intaxel was equally efficacious as Taxol, when it was combined with doxorubicin or carboplatin for the second line treatment for stage IV metastatic breast cancer. The bias which arises in the investigator or the patient is often a concern in open-label studies; however, it is unlikely that such a bias occurred in this study in the determination of the efficacy. If such biases would have played a role, we would have seen a superior betterment in the patients who were treated with the Taxol therapy, where the efficacy of the drug has been well established in clinical settings.

It was also observed that paclitaxel, in combination with either carboplatin or doxorubicin, was well tolerated by the patients. The safety profile of paclitaxel in our study was consistent with that of the previous reports [20-21]. A majority of the adverse effects which were noted in both the groups resolved without intervention and they had no further sequel. The majority of the adverse events were graded as mild or moderate in nature. The most common adverse effects which were observed in both the groups were alopecia and asthenia. Though they were not statistically significant, yet, clinically a larger number of patients who were on Taxol experienced adverse reactions as compared to those in the Intaxel group.

A statistically higher incidence of neurosensory loss was observed in the Taxol (8/24) group as compared to that in the Intaxel group (1/25). Also, a higher incidence of haematological toxicities was observed with the Taxol treatment as compared to the Intaxel treatment. Thus, for the haematological adverse events, Intaxel demonstrated a better safety profile as compared to Taxol, with a lower incidence of myelo-suppression. The most common adverse effect which needed medication was bone marrow toxicity, which was controlled with the use of the colony granulocyte stimulating factor.

No treatment related deaths were observed. One death was attributed to the disease progression. No cases of cardiotoxicity were observed in our study, as in few of the previously published studies [22-23]. The difference in the incidences of serious adverse events which were observed in both the groups was not statistically significant. The numbers of patients who discontinued the therapy due to adverse events were similar in both groups. To summarize, both the brands of paclitaxel, Intaxel and Taxol, had similar toxicity profiles.

In the present study, the patients who had received a prior anthracycline based chemotherapy were randomized to receive the carboplatin-paclitaxel combination only. This was done to improve the response to the treatment. The number, therefore, of the patients in the doxorubicin-paclitaxel group was low. This did not introduce any bias in the study, as the patients could still be randomized to the paclitaxel study drug (either Intaxel or Taxol). However, overall, the small number of patient enrollment was the limitation of this study.

CONCLUSION

In conclusion, our study showed a similar efficacy of Intaxel as compared to that of Taxol when it was combined with docetaxel or carboplatin as a second line treatment for stage IV breast cancer. The toxicities which were associated with the treatment were manageable. Overall, this study demonstrated that Intaxel and Taxol had comparable efficacies and safety profiles for metastatic breast cancer.

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FINANCIAL OR OTHER COMPETING INTERESTS:

None.

Date of Submission: **Jun 21, 2012**
Date of Peer Review: **Jul 21, 2012**
Date of Acceptance: **Mar 20, 2013**
Date of Publishing: **Jun 01, 2013**