Role of taxanes in the treatment of advanced NHL patients: A randomized study of 87 cases

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Abstract

NHL is a highly chemo-sensitive as well as radiosensitive disease. From May 2005 to June 2010, 87 patients were randomised into 2 arms. The control arm received the standard CHOP regimen + IFRT, whereas the study arm received Paclitaxel, 135/m^2 additionally. The results showed a better Overall Response (87% vs 78%) in the study arm. The 3yr and 5yr overall survival were significantly better in the study arm (89% vs 77%, p- value <0.05; 83% vs 67%, p-value <0.05). However, the incidence and severity of the side effects, haematological and non- haematological were enhanced but manageable in the study arm.

Keywords

Taxanes, Paclitaxel, Non Hodgkin's Lymphoma

Introduction

Since the last few decades, NHL, which is one of the most chemo-sensitive and uniquely radiosensitive malignancies, has been treated variously for better results. Majority of patients of NHL can be cured by CT alone- a known fact since last 30 years. Recently, advances in molecular medicine and cell surface antigen knowledge have led to newer approaches of CT.

The incidence of NHL is lowest in Asia[5]. The total estimated number of cases is 65,540 [1]: (Male: 35,380; Female: 30,160) and the total estimated deaths is 20,210 [1]: (Male: 10,710; Female: 9,500).

Taxane group of drugs are novel agents that act mainly through microtubule inhibition have already been proven to improve the results in relapsed, refractory and aggressive NHL cases[2,3] The encouraging results in the first line treatment of other malignancies (breast, non-small cell lung ca, and ovarian ca) also led to the use of paclitaxel in the management of advanced NHL cases.

Despite the improved survival curves in the present era of chemotherapy, the search for improvement continues. In this line, we studied the effects of adding Paclitaxel to the standard treatment protocols.

It is the aim of this study to determine the efficacy and safety profile of taxanes in the first-line management of advanced NHL cases and compare it to the standard CHOP regimen.

Patients and Methods

Between the period of May 2005 to June 2010, 92 cases reporting to the OPD at Radium Institute, Patna, India were selected. Inclusion criteria were Advanced stage (III & IV) NHL cases, Histopathologically proven, No prior treatment, No co-morbidity, KPS≥80, Hb% > 10gm/dl; TLC> 4000/dl; adequate platelets. The selected patients underwent the following investigations: CBC, Renal function tests, Liver function tests, Serum LDH, Cardiac ECG, Bone marrow examination/Bx, CXR- PA view, USG, CT Scan, MRI (where required).

Written and informed consent were taken from all patients.

Criteria for exclusion were: H/O other malignancy, cardiac disease, pre-existing motor/ sensory neuropathy, no consent, poor GC/ moribund cases.

The selected cases underwent thorough clinical examination and investigations, and then

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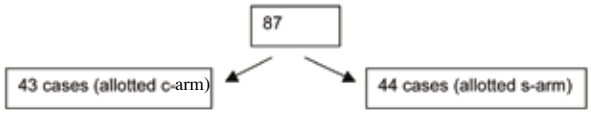
finally 87 patients were randomized for two arms of treatment and studied.



ARM I (c-arm): CHOP (6-8 cycles) + IFRT

ARM II (s-arm): CHOP + Paclitaxel (6-8 cycles) + IFRT

Doses (both arms): Cyclophosphamide: 750mg/m^2 IV D1; Adriamycin: 50mg/m^2 IV D1; Vincristine: 1.4mg/m^2 IV D1; Prednisolone: 100mg P.O. D1-D5, 3 weekly for 6-8 cycles

Paclitaxel was added in the doses of 135/m^2 IV infusion over 3 hrs on D1 in the s-arm.

Filgrastim and erythopoetin were administered as and when required. Premedication with 5- HT inhibitors, Proton Pump Inhibitor, Dexamethasone was done. Post-CT medication- Ondansetron 8mg x3 for 3 days; Dexamethasone oral/ iv, Pantoprazole 40mg OD for 3d; +symptomatic and supportive care and antibiotics were given.

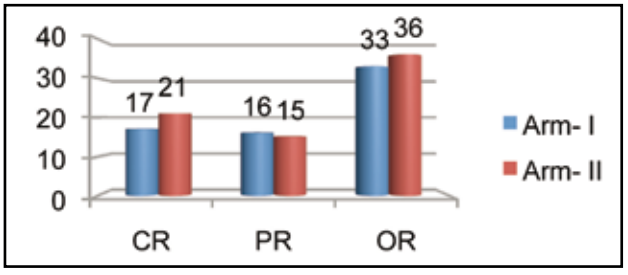
Radiotherapy: Involved Field Radiation Therapy (IFRT) was administered by the 60Co (780 Theratron) machine at the Radium Institute, PMCH, Patna. Dose: 40 Gy in 20# over 3-4 weeks. EBRT was given 2 wks after CT.

Results

The study arm showed a better Overall Response (82 vs 77%).

a) Reduction in the size of largest LN and number of site involved.

The reduction in the size of the largest disease site was more (95.4% vs. 88.3%), and also the reduction in the number of sites involved (85% vs. 82%) in the arm of study.



	CR(%)	PR(%)	OR(%)
C-arm	17(40)	16(37)	33(77)
S-arm	21(48)	15(34)	36(82)

Fig. 1: CR, PR, OR

		2 cycles	4 cycles	6 cycles	8 cycles	
C-Arm	N= 43	37.2%	60.4%	83.72%	88.3%(only 10 pt)	C-arm
S-Arm	N=44	45.45%	65.9%	90.90%	95.4%(only 8 pt)	S-arm

Table 1: Reduction in the largest LN involved

No of site inv	2cycles Residual(%)	4 cycles	6 cycles	8 cycles
209	157(75%)	113(54%)	65(31%)	38(18%)
212	131(62%)	100(47%)	55(26%)	32(15%)

Table 2: Reduction in the no. of site involved

b) Number of patients reporting at follow- up

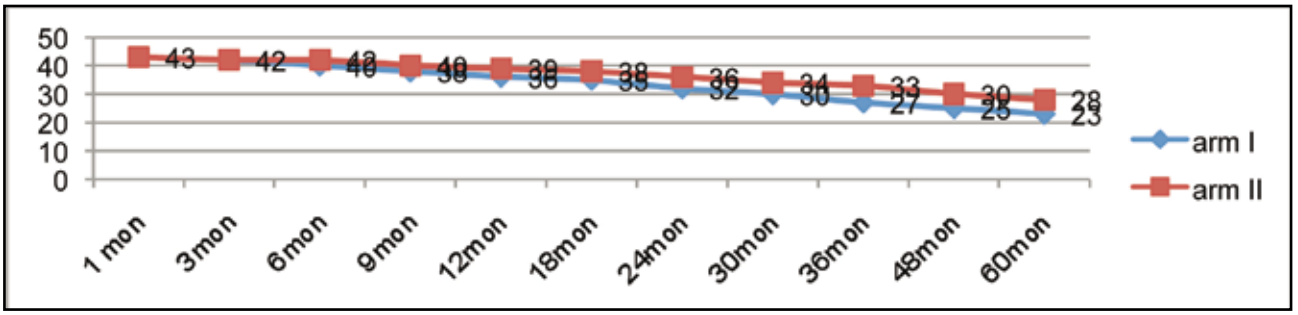


Figure 2: Patients reporting for follow up

c) Cumulative Overall Survival

A significant benefit in the 3 yr survival (77% vs. 89%; x2=5.10, p- value<0.05) as well as 5 yr survival (67% vs. 83%; x2=6.82, p-value <0.05).

d) Side Effects

The incidence and severity of the side effects, haematological and non- haematological were enhanced, but manageable in the study arm.

	C-arm	S-arm	Hazard ratio	P-value
Cumulative 3 yr survival	77%	89%	0.48	<0.05
Cumulative 5 yr survival	67%	83%	0.52	<0.05

Table 3: Cumulative OS

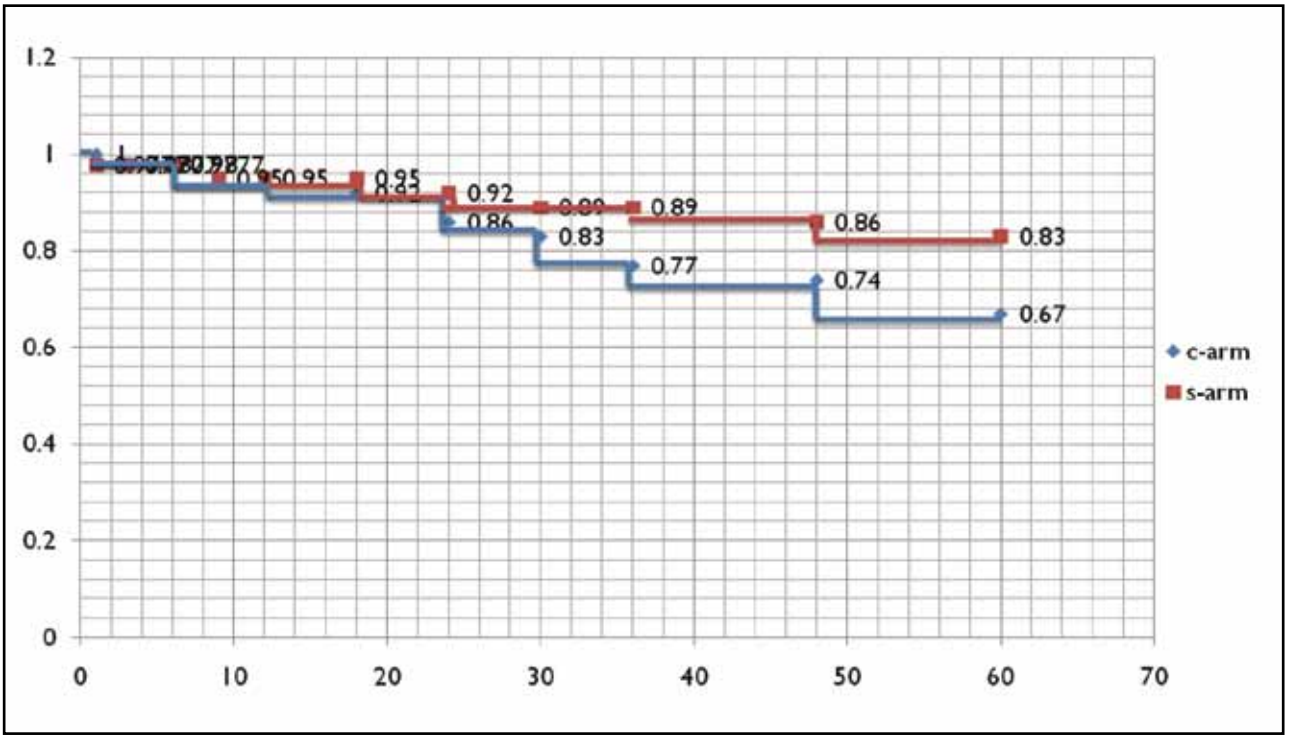


Figure 3: Cumulative survival curves for a follow up period of 5 years

Haematological toxicities:

Toxicity	grI		grII		grIII		grIV	
No. of cycles: 278/280	C-arm	S-arm	C-arm	S-arm	C-arm	S-arm	C-arm	S-arm
Anemia	11(4%)	14(5%)	58(21%)	56(20%)	22(8%)	28(10%)	1(0.005%	5(2%)
Neutropenia	29(10%)	33(12%)	41(15%)	30(11%)	22(8%)	90(32%)	0	28(10%)
thrombocytopenia	18(6%)	22(8%)	0	5(2%)	0	0	0	0

Table 4: Haematological toxicities

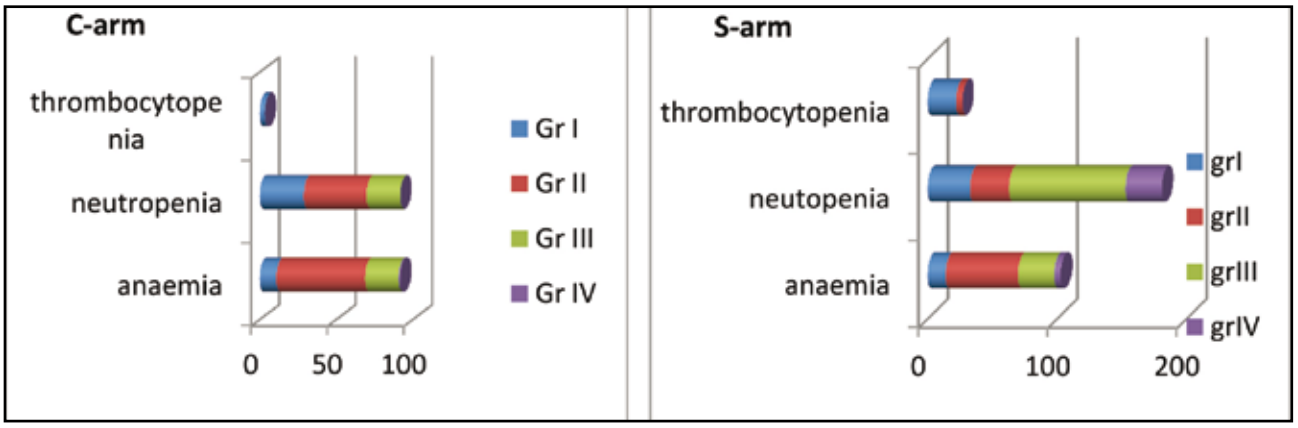


Figure 4: Haematological toxicities in both arms of study

Non-Haematological toxicities:

Non- haematological toxicity								
Toxicity	Gr I		Gr II		GrIII		Gr IV	
No of cycles: 278/280	Arm I	Arm II	Arm I	Arm II	Arm I	Arm II	Arm I	Arm II
Nausea/vomiting	61(22%)	68(24%)	58(21%)	73(26%)	00	6(2%)	00	00
Neuropathy	00	89(32%)	00	28(10%)	00	00	00	00
Mucositis	14(5%)	42(15%)	00	9(3%)	00	00	00	00
Diarrhea	29(10%)	33(12%)	3(1%)	15(5%)	00	00	00	00
Alopecia	2(5%)	00	41(95%)	44(100%)	00	00	00	00

Table 5: Non- Haematological toxicities

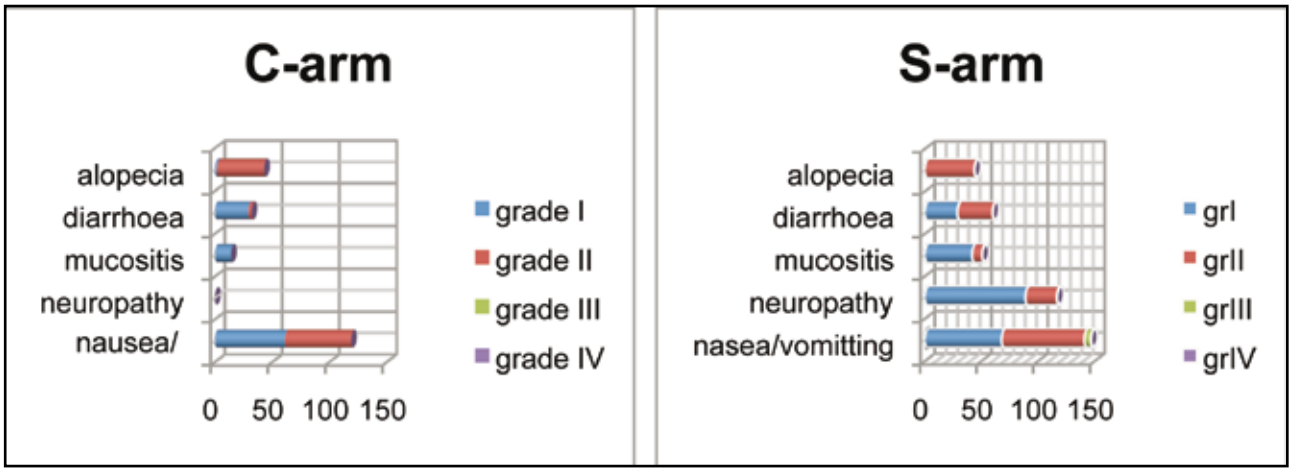


Figure 5: Non- Haematological toxicities in both the arms of study

Conclusion

This work concludes that Paclitaxel is a potent and effective drug in the first line management of advanced NHL cases. As per our study which still continuing, there is a clear-cut advantage of adding Paclitaxel to the existing CHOP + IFRT treatment protocol.

References

1. SEER cancer statistics review 1975-2007; Cancer Facts & Figures – 2010, American Cancer Society (ACS), Atlanta, Georgia, 2010.
2. Younes A, Ayoub JP, Sarris A, Paclitaxel activity for the treatment of non-Hodgkin's lymphoma: final report of a phase II trial, Br J Haematol. 1997 Feb; 96(2):328-32.
3. WH Wilson, BA Chabner, G Bryant, Journal of Clinical Oncology, Vol 13, 381-386, Copyright © 1995 by American Society of Clinical Oncology.
4. Chap 41: NHL\Devita 7th EDN\
5. Seow A, Lee J, Sng I, et al. Non-Hodgkin's lymphoma in an Asian population: 1968–1992 time trends and ethnic differences in Singapore. Cancer 1996;77(9):1899
6. Jemal A, Tiwari RC, Murray T, et al. Cancer statistics, 2004. CA Cancer J Clin 2004; 54(1):8.