

**EOSINOPENIA INDUCTION BY VINOURELBINE ALONE AND IN COMBINATION WITH DOXORUBICIN AND CISPLATIN IN CANCER PATIENTS**

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**Summary**

Eosinopenia is a kind of leukopenia associated with shortage of eosinophils. Its major causes included acute infectious stress, myelotoxic drugs, and leukemia. Chemotherapeutic agents obviously exert remedy along with toxic effects. This study aimed to investigate the alterations in Eosinophil count in cancer patients and was administered vinorelbine as part of their chemotherapy. A total 60 adult cancer patients were randomly divided in to two groups; Group-1 received the treatment of Vinorelbine alone and group 2 patients on Vinorelbine base combinations. Results showed significantly higher potential of eosinopenia induction in the patients on vinorelbine alone ( $p$  value  $<0.029$ ) as compare with the patient received vinorelbine based combinations ( $p$  value 0.759). The comparison of mean values of these two groups at every week indicated significant difference of eosinopenia at week-2 only (Mean  $\pm$ SEM:  $0.162759 \pm 0.032417$ ,  $p$  value 0.006). There was no significant difference observed in eosinopenia on comparison of mean values before therapy with that of week-4 (after therapy) in both of the groups. However, among the groups, the potential for induction of Eosinopenia is similar. Thus; in conclusion, there is no significant difference in the overall eosinopenia in both of the chemotherapy protocols. The clinical oncologist, consultant physician and pharmacist, can select either of the treatment plan.

**Keywords:** Eosinopenia, vinorelbine, cisplatin, doxorubicin, breast cancer and lung cancer

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### **Introduction**

Cancer of course is a fatal dilemma of human life and it was the more feared and in many ways, the most mysterious of the major life threatening diseases. It is being treated stereoscopically with good or bad results by using surgical, radiological or chemotherapeutical procedures. The eosinopenia is the main side effect of hematological toxicity cause during the treatment of certain cancerous conditions. It is associated with shortage of eosinophils and caused by acute infectious stress, myelotoxic drugs, and leukemia [1]. Vinorelbine is given for the treatment of breast cancer and non-small cell lung cancer. It is semi-synthetic vinca alkaloid obtained from the rosy periwinkle, *Catharanthus roseus*. Cisplatin, cisplatinum, or *cis*-diamminedichloroplatinum is a platinum-based drug used for the treatment of sarcomas, carcinomas, lymphomas, ovarian cancer and germ cell tumors. These platinum complexes react *in vivo*, binding to and causing crosslinking of DNA which ultimately triggers apoptosis (programmed cell death). Doxorubicin is an anthracycline antibiotic and works by intercalating DNA. The drug dates back to the 1950's when it was originally isolated from bacteria found in soil samples taken from Castel del Monte, an Italian castle. It is commonly used in the treatment of a wide range of cancers.

Thus; this study project is aimed because of the increased clinical value of vinorelbine, cisplatin and doxorubicin used in the treatment of certain cancerous conditions. The Eosinopenia caused by vinorelbine alone and its combinations (with doxorubicin and cisplatin) was investigated pre & post chemotherapy to evaluate their clinical credibility.

### **Materials and Methods**

The study was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Center (SKMCH&RC), M.A Johar town, Lahore, Pakistan to investigate the changes in Eosinophil count of adult cancer patients with Non small cell lung cancer, metastatic breast cancer, and of cervix, treated with Vinorelbine alone, Vinorelbine/ Doxorubicin and Vinorelbine/Cisplatin treatment protocols.

#### ***Study Design***

These patients were selected from outpatient department (OPD) of SKMCH&RC who were diagnoses as breast cancer, NSCLC and cancer of cervix belong to any age group, had ether sex and consented for this study. An exclusion criterion is involvement of patient in any other study. A total 60 cancer patients were divided into two groups; Group-1 comprising of patient received vinorelbine as single therapy and Group-2 having the cancer patients on treatment protocol of vinorelbine based combinations i.e. Vinorelbine/ Cisplatin or vinorelbine/ Doxorubicin (Table1).

#### ***Preparations of Standard Regimen of Chemotherapeutical Agents***

The standard treatment regimen for vinorelbine, cisplatin and doxorubicin is reported by Nazir et al, [2] [3]. The vinorelbine was administered 25 mg/ml on day 1, weekly 4, i/v, with 0.45% sodium chloride or 5% glucose solution as diluents and delivered over

intravenous push (IVP) [4]. The injected dose infused over a short period -15 to 20 minutes [5]. In combination therapy the dose of Vinorelbine was decreased and administer as 20 mg/ml on day 1, 8 I/V with diluent day 5 ½ normal saline and delivered over IVP. The Doxorubicin was given as 50 mg/m<sup>2</sup> on day 1 only [6]. Doxorubicin was administered slowly in to tubing of freely running infusion of Sodium Chloride 0.9% or Glucose 5%. [7]. The Cisplatin was administered intra-venously as 40mg/ml on day 1 only, with the diluent of day 5 ½ NS and delivered over IVP.

**The chemotherapy protocols follow up schedule and cancer site of experimental patients**

Group	Sample size	Chemotherapy protocol	Patient neoplasm type	Chemotherapy schedule (days)	Follow up schedule (days)
<b>G-I</b>	45	Vinorelbine	Metastatic breast cancer	1,7, 14, 21	6, 13, 20, 28
			NSCL cancer	1, 7, 14, 21	6, 13, 20, 28
<b>G-II</b>	15	Vinorelbine/ Doxorubicin	Metastatic breast cancer	1, 8	7, 15
		Vinorelbine/ cisplatin	NSCL cancer	1, 8	7, 15
			Cervix Cancer	1, 8	7, 15

***Sample Collection and Eosinophil Count:***

The 3ml of blood samples were drawn from brachial veins in 5 cc disposal syringes and transferred to appropriately labeled (complete blood count (C.B.C) vials containing 20 w/v of EDTA. The eosinophil count was performed using a computerized auto-analyzer (Technicon 113, Bayer Laboratories USA) at the Pathology laboratory, SKMCH&RC.

***Data Analysis***

The means of two groups were compared by student t-Test to avoid the consistent deviation of analytical results or systematic errors in the procedure. ANOVA used to identify any factor influencing the test results.

**Result and Discussion**

The effect of different treatments on eosinophil count is given in Table 1. On week 1, 3 and 4 of the treatment no significant difference in eosinopenia was observed. However as shown by the eosinophil count on week 2, significant difference in the potential for eosinopenia was observed. When the mean eosinophil counts before therapy (Week 0)

were compared with that of after therapy (week 4), there no any significant decrease was noted in the patients on either of treatment protocol.

**The mean  $\pm$ SEM Eosinophil count ( $\times 10^3$ ) per ul, pre and post chemotherapy of cancer patients on the treatment protocol of vinorelbine (Group I), vinorelbine based combinations (Group II) and overall total (60) patients.**

Time (week)	Vinorelbine (Group-I)		Vinorelbine in combination (Group-II)		Overall		P value <sup>3</sup>
	Mean	SEM	Mean	SEM	Mean	SEM	
<b>Week 0</b>	0.18547	0.028292	0.149333	0.03435	0.175965	0.02267	0.488
<b>Week 1</b>	0.195814	0.042473	0.068	0.012806	0.162759	0.032417	0.006
<b>Week 2</b>	0.129856	0.022181	0.072666	0.018859	0.114464	0.017258	0.145
<b>Week 3</b>	0.11378	0.0240037	0.054166	0.044477	0.099184	0.018628	0.171
<b>Week 4</b>	0.116333	0.0296434	0.09666	0.038188	0.11179	0.024259	0.738
<b>P value<sup>1</sup></b>	0.029		0.759		0.045		
<b>P value<sup>2</sup></b>	0.102		0.665				

P value<sup>1</sup>; represent overall comparison of mean values over time,

P value<sup>2</sup>; represent the independent comparison of mean values for two groups at every week

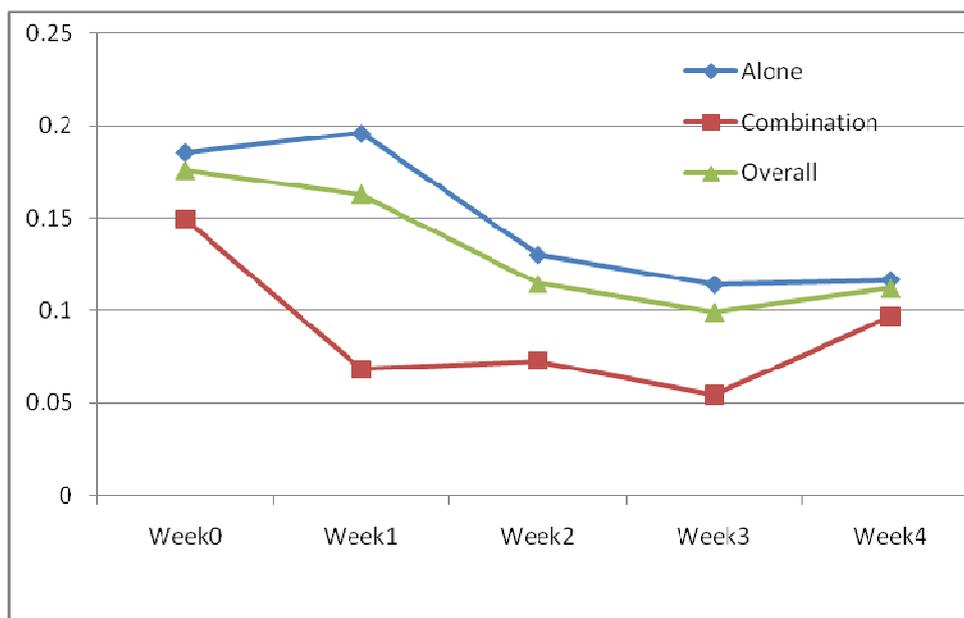
P value<sup>3</sup>; represent comparison of mean values observed before therapy with that of week 4 (after therapy)

$p < 0.001$  considered extremely significant and  $p < 0.05$  considered significant

All values are expressed in Mean  $\pm$  SEM, n = 60

Our finding are in line with Takimoto et al., [8], who reported a patient with aplastic large-cell lymphoma (Ki-1 lymphoma) showing eosinophilic invasion of the tumor tissues. The number of eosinophils in the peripheral blood changed as a function of the stage of the disease. The IL-5 gene was expressed in the tumor tissues, suggesting that the eosinophilic invasion and eosinophilia were caused by IL-5 derived from the lymphoma cells.

Dorr et al [9] reported the dose limiting leucopenia of oral vinorelbine. Marty et al. [10], concluded the leucopenia as noncumulative and of short duration (<7 days). While Shamseddine et al, [11] reported the cisplatin and vinorelbine combination therapy having acceptable hematological toxicities.



**Figure 1. Mean Eosinophilic count (in 000) Vs time (in weeks)**

Niiya et al., [12] reported doxorubicin used for the treatment of lung cancer in Japan. They investigated the effects of AMR (Amurubicin hydrochloride) on the expression of uPA (urokinase-type plasminogen activator) and chemokines in NCI-H69 cells. When the cultured supernatant obtained from AMR-treated H69 cells was subcutaneously injected into rabbits, migration of a significant number of eosinophils was observed around the injected site. The induction was observed below the clinically achievable concentration of AMR or AMROH. Which may play a role in the pharmacological action of AMR through induction of the interaction between proinflammatory cells and lung carcinoma cells.

Faller et al., [13] reported the cisplatin-based chemotherapy has become an accepted standard in the adjuvant treatment of non-small-cell lung cancer (NSCLC). They present a case of acute myelogenous leukemia with an 11q23/MLL rearrangement diagnosed 1 year after the completion of 4 cycles of cisplatin and vinorelbine for resected NSCLC. This case of therapy-related acute myelogenous leukemia (t-AML) associated with this chemotherapy combination. The literature on t-AML with the 11q23/MLL rearrangement is reviewed.

### Conclusion

In conclusion, there were no significant differences observed in the overall eosinophilic toxicity of both of the chemotherapy protocols. Therefore the therapeutical efficacy should constitute the overall consideration of treatment of breast, cervix and non small cell lung cancers.

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