BASOPENIA INDUCTION BY VINORELBINE ALONE AND IN COMBINATION WITH DOXORUBICIN AND CISPLATIN IN CANCER PATIENTS

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ABSTRACT

The anticancer drugs used in cancer therapy exerts cure along with deleterious effects. They bring structural and physiological changes in vital organs. Basopenia or basocytopenia is one of the major side effects of antineoplastic agents. This study therefore aimed to investigate the alterations in basophile count in cancer patients administered vinorelbine, cisplatine and doxorubicin as part of their chemotherapy protocols. The pharmacovigilance study or post marketing therapeutical monitoring become important when the drugs are part of certain cancer chemotherapy plans. A total 60 adult patients were randomly divided in to two groups; Group-1 received the Vinorelbine alone and group 2 patients on Vinorelbine base combinations. Results showed significantly lower potential of basopenia in the patients on vinorelbine alone (*p* value 0.435) vinorelbine base combinations (*p* value 0.437). The comparison of mean values of these two groups at every week indicated no difference of the chance of basopenia (*p* values Week 0-4: 0.517, 0.089, 0.434, 0.475 and 0.275). Similarly no significant difference was observed in the basophile count before therapy and after therapy (at week-4) in both of the groups ((*p* value for G-1: 0.221 and G-2: 0.314). However, among the groups, the potential for induction of basopenia is similar. Thus; in conclusion, there is no significant difference in the overall basopenia in both of the chemotherapy protocols. The clinical oncologist and consultant physician can select either of the treatment plan.

INTRODUCTION

Cancer is the more feared and in many ways, the most mysterious of the major life threatening diseases. It is a fatal dilemma and is still remained a very real concern to public health. Miscellaneous treatment procedures and protocols used stereoscopically with good or bad results (Kuby, 1994). Basopenia (or basocytopenia) is one of the hematological adverse effects of antineoplastic drugs vinorelbine, cisplatin and doxorubicin. It is a form of agranulocytosis associated with a deficiency of basophils (Biologyonline, 2010). It is difficult to evaluate due to the small and variable number of basophilic granulocytes normally present in the blood (Definitions online, 2009). In humans, the condition of basopenia is notice if basophile count is less than 0.01 x 10^{9}/L (Pathology, 2010). It is difficult to detect without flow cytometry, because normal levels are very low (Soni et al., 1996). Thus; a continuous therapeutical surveillance

(pharmacovigilance or phase IV clinical trial of post marketing safety monitoring) usually desired to optimize the anti-neoplastic treatment protocols (Taha, 2009). It specially becomes more important to study the basopenic effect of vinorelbine, cisplatin and doxorubicin, because of their sufficiently utilization in clinical practice of cancer chemotherapy.

Thus; this study project is aimed because of the increased clinical value of vinorelbine, cisplatin and doxorubicin used in treatment of certain cancerous conditions. The basopenia caused by vinorelbine alone and its combinations (Vinorelbine/ Doxorubicin and Vinorelbine 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 basophile 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.*,2009. The vinorelbine was administered 25 mg/ml on day 1, weekly 4, i/v, with 045% sodium chloride or 5% glucose solution as diluents and delivered over intravenous push (IVP) (Kubota K., 2000). The injected dose infused over a

short period -15 to 20 minutes (Reynald, et al 1996). 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/m2 on day 1 only (Fauzia 2000). Doxorubicin was administered slowly in to tubing of freely running infusion of Sodium Chloride 0.9% or Glucose 5%. (USPDI, 1997). 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.

Table 1: The chemotherapy protocols follow up schedule and cancer site of experimental patients- Sample Collection and Basophile Count:

Grp	S Size	Ch. protocol	Patient neoplasm type	Chem ther sched (d)	Follow up sched (d)
G-I	45	Vinorelbine	Metastatic breast cancer	1,7, 14, 21	6, 13, 20, 28
			NSCL cancer	1, 7, 14, 21	6, 13, 20, 28
G-II	15	Vinorelbine/ Doxorubicin	Metastatic breast cancer	1, 8	7, 15
		Vinorelbine/ cisplatin	NSCL cancer	1, 8	7, 15
			Cervix Cancer	1, 8	7, 15

Samples collection detail also available at Taha *et al.*,(2009) and Taha et al., (2010). 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 basophile 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

The effect of different treatments on basophile count is given in Table 1. During any week of the treatment no significant difference in basopenia was observed. When the mean basophile 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.

DISCUSSION

The finding of this study are in line with the work of Shamseddine *et al.*,(1999), who reported low potential of basopenia with either of the chemotherapy protocols along with acceptable hematological toxicities of cisplatin and vinorelbine combination therapy. Dorr et al (1994), reported the dose limiting leucopenia of oral vinorelbine without significant potential of basopenia. Marty et al. (1989), also reported noncumulative basopenia of short duration (<7 days). Moreover, Khynriam et al (2001) reported the cisplatin-mediated development of various hematological changes in mice bearing ascites (Dalton lymphoma tumor). Cisplatin treatment of tumor-bearing mice reduces eosinophils, basophils, and lymphocytes along with the development of various morphological abnormalities. However, combination treatment of cysteine plus cisplatin resulted in lower the potential of hematological toxicities.

In addition of that Krasnozhenov (1994) also reported the influenced of doxorubicin upon the morphofunctional state of the peritoneal, mesenteric and dermal tissue basophils which was evident from changes in the total number of the mast cells and the level of their maturity, activity and ability to respond to con A and the antigen. In the late periods after the completion of the treatment with the cytostatic the quantitative changes were slightly pronounced and the functional activity remained high for 3 months. Predisposition to allergic reactions was confirmed by positive intracutaneous tests with horse serum albumin.

Table 2: The mean ±SEM Basophiles count ($\times 10^3$) per µl, 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[2]
	Mean	SEM	Mean	SEM	Mean	SEM	
Week 0	0.058	0.021	0.035	0.007	0.052	0.015	0.517
Week 1	0.030	0.002	0.022	0.002	0.028	0.001	0.089
Week 2	0.031	0.004	0.025	0.000	0.029	0.003	0.434
Week 3	0.038	0.010	0.025	0.002	0.035	0.007	0.475
Week 4	0.026	0.003	0.022	0.002	0.025	0.006	0.275
P value[1]	0.435		0.437		0.289		
P value[3]	0.221		0.314				

P value[1] represent overall comparison of mean values over time,

P value[2] represent the independent comparison of mean values for two groups (G-I & G-II) at every week

P value[3] represent comparison of mean values observed before therapy with after therapy (week 4) of both Groups ((G-I & G-II)).

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

All values are expressed in Mean ± SEM, n = 60

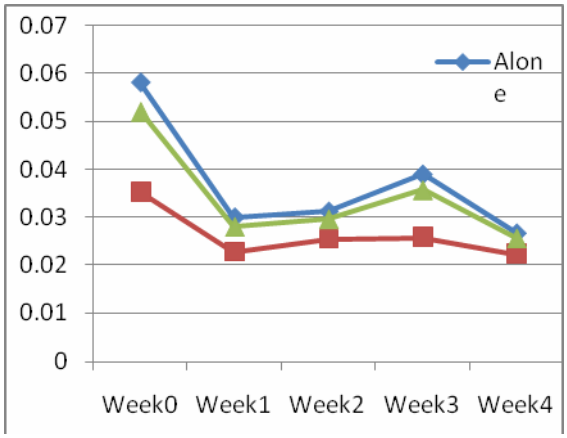

Figure 1 Mean Basophiles count x1000/µl Vs time (in weeks).

CONCLUSION

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

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