



Research Article

Potential Leukocytic Toxicity Induce by Vinorelbine, Doxorubicin and Cisplatin in Human Patients of Breast, Cervix and Lung Cancer

Taha Nazir^{1,2}, Nida Taha², Muzhar Mustafa³, Azharul Islam⁴, Adeel Mahmood⁵ and Saeed ur Rasheed Nazir⁶

Abstract

Anticancer drugs are used extensively in chemotherapy. Bone marrow suppression is one of their major side effects. Therefore, we aimed this study to investigate the potential leukocytic toxicity induced by vinorelbine in cancer patients. The data of total 60 adult patients were selected and divided into two groups; Group-1 patients received Vinorelbine alone and group-2 Vinorelbine based combinations. The outcomes demonstrated no statistically important difference in the patients who were either on vinorelbine alone, vinorelbine plus cisplatin or vinorelbine plus doxorubicin combinations. On comparison of mean value SEM \pm count (10^3) Per μ L overtime pre & post chemotherapy, no statistical differences were observed in Basophil and Lymphocyte counts for Group-I; Eosinophil, Basophil, Monocyte, and Lymphocyte counts for Group-II. Comparison of mean values \pm SEM ($\times 10^3$) per μ L before therapy with that of at week-4 (pre and post chemotherapy) showed no significant difference in Eosinophil, Basophil and Lymphocyte counts for Group-I (*P* value 0.102, 0.221, 0.063); and TLC, Neutrophil, Eosinophil, Basophil, Monocyte and Lymphocyte counts (*P* value 0.148, 0.118, 0.665, 0.314, 0.053, 0.427) for Goup-II. Hence, the overall Leukocytopenia, Neutropenia, Eosinopenia, Basopenia, Monocytopenia and Lymphocytopenia in both of the chemotherapy protocols allow the clinical oncologists and consultant physicians to select either of the chemotherapeutic agents. The therapeutic efficacy should constitute the intervening consideration in treating the patients of breast, cervix and lung cancer.

Keywords

Leukocytopenia; Leucopenia; Vinorelbine; Cisplatin; Doxorubicin; Breast cancer; NSCLC

Introduction

Cancer is a fatal dilemma of human life and more mysterious of the major life threatening diseases. Despite of the scientific miracles, cancer is still a very real concern to public health, both in perception and reality. It is being treated stereoscopically with good or bad results by using surgical, radiological or chemotherapeutic methods [1].

*Corresponding author: Taha Nazir, Research Associate, Biochemistry, Chemical Pathology, Molecular & Microbiology Research Group, University Medical & Research Centre, University of Sargodha, Sargodha 40100 Pakistan, Tel: +92 321 222 0885; E-mail: tahanazir@yahoo.com

Received: June 22, 2015 Accepted: July 20, 2015 Published: July 23, 2015

There are several types and stages of chemotherapy used to treat cancer; induction therapy, consolidation therapy, intensification therapy, maintenance therapy, adjuvant therapy, palliative therapy and chemo preventive therapy [2]. We have focused over the chemotherapy of any type and stage of patient diagnosed as cancer; the leukocytic toxicities produced by Vinorelbine alone and combinations.

Materials and Methods

This retrospective study was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Center (SKMCH&RC), M.A Johar town, Lahore, Pakistan. We have collected the information's of Non-small cell lung cancer, metastatic breast cancer, and cervix cancer patients, taken Vinorelbine alone, Vinorelbine/ Doxorubicin and Vinorelbine/Cisplatin treatment protocols. Our major goal was to investigate the changes in leukocytic laboratory profile of human cancer patients.

Study design

These patients were selected from outpatient department (OPD) of SKMCH&RC. The patients' selection criterion was including as under;

1. Should be differentially diagnosed the neoplasm.
2. Patients with Metastatic breast / NSCL/ Cervix Cancer
3. Patients took vinorelbine as part of their treatment in clinical setting.
4. Having no history of blood or liver disease
5. Either sex of male or female.

Similarly, an exclusion criterion was also designed to scrutinize the patient for this 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 (Table 1).

Table 1: 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)
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

Preparations of standard regimen of chemotherapeutical agents

The standard treatment regimen for vinorelbine, cisplatin and doxorubicin is reported by Taha et al. [3,4]. 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) [5]. The injected dose infused over a short period -15 to 20 minutes [6]. In combination therapy the dose of Vinorelbine was decreased and administer as 20 mg/ml on day 1, 8 I/V with diluents day 5½ normal saline and delivered over IVP. The Doxorubicin was given as 50 mg/m² on day 1 only [7]. Doxorubicin was administered slowly in to tubing of freely running infusion of Sodium Chloride 0.9% or Glucose 5% [8]. The Cisplatin was administered intra-venously as 40 mg/ml on day 1 only, with the diluent of day 5½ NS and delivered over IVP.

Sample collection and neutrophils count

The 3 ml 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 as described by Taha et al. [3]. The neutrophils 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. The obtained p values of Group-I, Group-II and overall (60) patients were compared before, after and every week to identify potential leukocytopenia.

Result

Comparison of mean value SEM ± count (10³) Per uL overtime pre & post chemotherapy showed no statistical differences were observed in Basophil and Lymphocyte counts (P value 0.435, 0.64) for Group-I; Eosinophil, Basophil, Monocyte, and Lymphocyte counts (P value 0.759, 0.437, 0.08, 0.23) for Group- II (Table 2). On comparison of mean values ± SEM (x10³) per µL before with that of a week-1,2,3,4 and 5 indicate no significant difference in TLC (P value 0.607, 0.944, 0.897); Neutrophil (P value 0.742, 0.208, 0.425, 0.048, 0.791); Eosinophil (P value 0.488, 0.145, 0.171, 0.738); Basophil (P value 0.517, 0.089, 0.434, 0.475, 0.270); Monocyte (P value 0.551, 0.112, 0.559, 0.372, 0.468); and Lymphocyte (P value 0.736, 0.555, 0.727) (Table 3). Comparison of mean values ± SEM (x10³) per uL before therapy with that of at weeeek-4 (pre and post chemotherapy) showed

Table 2: Comparison of P values of cancer patients on treatment protocol of Vinorelbine (Group-I), Vinorelbine based combination (Group-II) and overall (60) patients. P value obtained by overall comparison of mean values, overtime pre & post chemotherapy. p< 0.001 considered extremely significant and p < 0.05 considered significant All values are expressed in Mean ± SEM, n=60.

Study Parameter	G-1	G-2	Overall
Mean SEM ± TLC count (10 ³) Per uL	<0.001	<0.016	<0.001
Mean SEM ± Neutrophil count (10 ³) Per UI	<0.001	<0.028	<0.001
Mean SEM ± Eosinophil count (10 ³) Per uL	0.029	0.759	0.045
Mean SEM ± Basophil count (10 ³) Per uL	0.435	0.437	0.289
Mean SEM ± Monocyte count (10 ³) Per uL	0.001	0.08	0.001
Mean SEM ± Lymphocyte count (10 ³) Per uL	0.064	0.23	0.007

Table 3: Comparison of P values* of two groups at every week pre and post chemotherapy by cancer patients on treatment protocol of Vinorelbine (Group-I), Vinorelbine based combination (Group-II) and overall total (60) patients *P value obtained by the independent comparison of means values p< 0.001 considered extremely significant and p < 0.05 considered significant All values are expressed in Mean ± SEM, n=60.

Study Parameter	P Value 1 st Wk	P Value 2 nd Wk	P Value 3 rd Wk	P Value 4 th Wk	P Value 5 th Wk
Mean SEM ± TLC count (10 ³) Per uL	0.607	0.014	0.944	0.024	0.897
Mean SEM ± Neutrophil count (10 ³) Per UI	0.742	0.208	0.425	0.048	0.791
Mean SEM ± Eosinophil count (10 ³) Per uL	0.488	0.006	0.145	0.171	0.738
Mean SEM ± Basophil count (10 ³) Per uL	0.517	0.089	0.434	0.475	0.270
Mean SEM ± Monocyte count (10 ³) Per uL	0.551	0.112	0.559	0.372	0.468
Mean SEM ± Lymphocyte count (10 ³) Per uL	0.736	0.003	0.033	0.555	0.727

no significant difference in Eosinophil, Basophil and Lymphocyte for Group-I (P value 0.102, 0.221, 0.063); and TLC, Neutrophil, Eosinophil, Basophil, Monocyte and Lymphocyte (P value 0.148, 0.118, 0.665, 0.314, 0.053, 0.427) for Goup-II (Table 4).

The significant statistical differences were noted at every week pre and post chemotherapy in the mean (10³) per uL counts of neutrophil, Eosinophil & Lymphocyt at week 2 (P value 0.014, 0.006 & 0.003); Lymphocyte at week 3 (P value 0.033); and Leukocyte & neutrophil at week 4 (P value 0.024 & 0.048) (Table 3).

In addition of that, on comparison of the mean SEM ± counts (10³) Per µL before therapy with that of at weeeek-4, no significant statistical differences were observed in Eosinophil, Basophil, & lymphocyte (P values 0.102, 0.221 & 0.063) in Group-1; and Leukemia, Neutropenia, Eosinopenia, Basopenia, Monocytopenia & Lymphocytopenia (P values 0.148, 0.118, 0.665, 0.314, 0.053 & 0.427) in Group-2 (Table 4).

Discussion

The findings under discussion are in line with the work Dorr et al. [5], who reported the dose limiting leucopenia of Vinorelbine. Marty et al. [9] reported the leucopenia as noncumulative and of short duration (<7 days). While Shamseddine et al. [8] reported the acceptable degree of leukocytopenia induced by Cisplatin and Vinorelbine. Misako et al. [10] reported doxorubicin used for the treatment of lung cancer in Japan. The effects of AMR (Amurubicin hydrochloride) investigated over cultured supernatant. The subcutaneously injected into rabbits introduced a significant decline in number of eosinophil around the injected site.

Moreover, Kharbangar et al. [11] and Cao et al. [12] reported the cisplatin mediated development of various hematological changes in mice bearing ascites (Dalton lymphoma tumor). Cisplatin treatment of tumor bearing mice reduces eosinophil, 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.

Faller et al. [13] reported the accepted standard of cisplatin adjuvant chemotherapy of non-small-cell lung cancer (NSCLC) patients. Cisplatin and vinorelbine administered for acute myelogenous leukemia and NSCLC.

In addition of that Sauer et al. [14] reported the incidences of

Table 4: Comparison of P values* observed before therapy with that of at weeek-4 pre and post chemotherapy of cancer patients on the treatment protocol of Vinorelbine (Group-I) and Vinorelbine based combinations (Group-II) *P Value obtained by the comparison of means values observed before therapy with that of at weeek-4 pre and post chemotherapy. p<0.001 considered extremely significant and p<0.05 considered significant All values are expressed in Mean ± SEM, n=60.

Mean SEM ± TLC count (10 ³) Per uL	0.001	0.148
Mean SEM ± Neutrophil count (10 ³) Per UI	0.001	0.118
Mean SEM ± Eosinophil count (10 ³) Per uL	0.102	0.665
Mean SEM ± Basophil count (10 ³) Per uL	0.221	0.314
Mean SEM ± Monocyte count (10 ³) Per uL	0.001	0.053
Mean SEM ± Lymphocyte count (10 ³) Per uL	0.063	0.427

leucopenia with different response rate induced by two vinorelbine combinations; Vinorelbine, cisplatin, rh-endostatin and Vinorelbine, cisplatin. The collected information's from different databases were analyzed by Cochran systematic review methods and the meta-analysis conducted through software RevMan 5.0. Brown et al. [15] and Oostendorp et al. [16] reported the potential therapeutically benefits of vinorelbine and doxorubicin in clinical practice. These were selected for breast cancer patient because of their wide range of anticancer benefits. The studies randomly compared the drugs in combination with targeted agents to provide reasonable scientific evidences for therapeutically usage in advanced breast cancer patients.

Conclusion

There were no significant differences in the overall hematological toxicities of both of the chemotherapy protocols. The consultant oncologist can select either of the protocol to provide maximum relief to patients by assuring successful treatment. Moreover the therapeutically efficacy should probably constitute the overall consideration while treating the particular neoplasm.

References

- ACC (1999) Pharmacy Formulary and the Therapeutic Index. Division of Pharmacy LEXI Comp Inc USA 50-51.
- Farhat FS, Ghosn MG, Kattan JG (2015) Oral vinorelbine plus cisplatin followed by maintenance oral vinorelbine as first-line treatment for advanced non-small cell lung cancer. *Cancer Chemother Pharmacol*.
- Nazir T, Islam A, Omer MO, Mustafa M (2015) Lymphocytopenia; induced by vinorelbine, doxorubicin and cisplatin in human cancer patients. *Breast Dis* 35: 1-4.
- Liu D, Zheng X, Chen J, Liu G, Xu Y, et al.(2015) Induction chemotherapy with cetuximab, vinorelbine-cisplatin followed by thoracic radiotherapy and concurrent cetuximab, vinorelbine-cisplatin in patients with unresectable stage III non-small cell lung cancer. *Lung Cancer*. doi: 10.1016/j.lungcan.2015.06.004.
- Dorr TR, Daniel D, Hoffvon (1994) *Cancer Chemotherapy Handbook*. Appleton & Lange USA 286-292.
- USPDI (1997) Advice for patient drug information in lay. Tein Book Parkway Rockville Maryland 719-721.

- Subramanyan S, Abeloff MD, Bond SE, Davidson NE, Fetting JH, et al. (1999) A phase I/II study of vinorelbine, doxorubicin, and methotrexate with leucovorin rescue as first-line treatment for metastatic breast cancer. *Cancer Chemother Pharmacol* 43: 497-502.
- Shamseddine AI, Taher A, Dabaja B, Dandashi A, Salem Z, et al. (1999) Combination cisplatin-vinorelbine for relapsed and chemotherapy-pretreated metastatic breast cancer. *Am J Clin Oncol* 22: 298-302.
- Marty M, Extra JM, Espie M, Leandri S, Besenval M, et al. (1989) Advances in vinca-alkaloids: Navelbine. *Nouv Rev Fr Hematol* 31: 77-84.
- Misako Shibakura, Kenji Niiya, Toru Kiguchi, Isao Kitajima, Masami Niiya, et al.(2002) Induction of IL-8 and monocyte chemoattractant protein-1 by doxorubicin in human small cell lung carcinoma cells. *International Journal of Cancer* 103 DOI: 10.1002/ijc.10842.
- Kharbanger A, Khyriam D, Prasad SB (2000) Effect of cisplatin on mitochondrial protein, glutathione, and succinate dehydrogenase in Dalton lymphoma-bearing mice. *Cell Biol Toxicol* 16: 363-373.
- Cao D, Ge W, Wang H, Zhang L, Zheng Y, et al. (2011) [Efficacy and safety of rh-endostatin combined with chemotherapy versus chemotherapy alone for advanced NSCLC: a meta-analysis review]. *Zhongguo Fei Ai Za Zhi* 14: 404-413.
- Faller BA, Robu VG, Borghaei H (2009) Therapy-related acute myelogenous leukemia with an 11q23/MLL translocation following adjuvant cisplatin and vinorelbine for non-small-cell lung cancer. *Clin Lung Cancer* 10: 438-440.
- Sauer R, Fietkau R, Wittekind C, Rödel C, Martus P, et al. (2003) Adjuvant vs. neoadjuvant radiochemotherapy for locally advanced rectal cancer: the German trial CAO/ARO/AIO-94. *Colorectal Dis* 5: 406-415.
- Brown T, Pilkington G, Bagust A, Boland A, Oyee J, et al. (2013) Clinical effectiveness and cost-effectiveness of first-line chemotherapy for adult patients with locally advanced or metastatic non-small cell lung cancer: a systematic review and economic evaluation. *Health Technol Assess* 1-278.
- Oostendorp LJ, Stalmeier PF, Donders AR, van der Graaf WT, Ottevanger PB (2011) Efficacy and safety of palliative chemotherapy for patients with advanced breast cancer pretreated with anthracyclines and taxanes: a systematic review. *Lancet Oncol* 12: 1053-1061.

Author Affiliations^{Top}

¹Biochemistry, Chemical Pathology, Molecular & Microbiology Research Group, University Medical & Research Centre, University of Sargodha, Sargodha 40100 Pakistan

²Intellectual Consortium of Drug Discovery & Technology Development Incorporation, Saskatoon SK Canada S7L3E4

³Operations Manager, Emirates Medical Services, Fujairah, UAE

⁴Department of Pathobiological Sciences, Louisiana State University, Baton Rouge, Louisiana 70803 USA.

⁵Department of Biosciences, COMSATS Institute of Information Technology, Islamabad, PO; 45550, Pakistan

⁶Discipline of Social and Administrative Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, 11800