STUDY OF THE ANEMIC SYNDROME INDUCED BY VINORELBINE, DOXORUBICIN AND CISPLATIN IN HUMAN CANCER PATIENTS

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Summary

Cancer is fatal dilemma of human life. During the recently ended 20th century, it was the more feared and in many ways, the most mysterious of the major life threatening diseases. Despite of surprising advancement in applied therapeutics, cancer is still, both in perception and reality, a very real concern of public health. The present study was carried to investigate the hematological alteration in the patient diagnosis as cancer and was administered vinorelbine as part of their chemotherapy at Shaukat Khanum Memorial Cancer Hospital and Research Center, Lahore (Pakistan). A total of 60 adult cancer patients selected with non-small cell lung cancer(NSCL), metastatic breast cancer (MBC), and cancer of cervix, with age between 24 - 71 years (Mean 42.73, SEM±2.). They were divided in to two groups: Group-1 patients on the treatment protocol of Vinorelbine alone and group 2 patients on treatment protocol of Vinorelbine base combinations; Vinorelbine/ Doxorubicin and Vinorebine/ Cisplatin. The results obtained were statically analyzed. On comparison of overall mean values over time, the significant anemia and decreased hematocrit value were observed in the patients on chemotherapy protocol of Vinorebine alone and significant anemia and decreased hemoglobin concentration and hematocrit values observed in the patient of chemotherapy protocol of Vinorelbine based combination. By an independent comparison of Mean Values of these two group at every week, there were no significant toxicities observed in the patients on treatment protocol vinorelbine based combinations. When mean values observed before therapy compared to that of at week-4 of both of the groups, there were significant decreases noted in erythrocyte count, hematocrit value and hemoglobin concentration. In conclusion, there were insignificant differences in the overall anemic syndrome observe in both of the chemotherapy protocols. The clinical oncologist, consultant physician and pharmacist, therefore can probably select either of the chemotherapy protocol. The therapeutic efficacy probably should constitute the overriding consideration in treating a particular neoplasm.

Keywords: Vinorelbine, Cisplatin, Doxorubicin, breast cancer, NSCLC- non small cell lung cancer, erythrocyte count, hematocrit value, hemoglobin concentration.

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Introduction

Cancer is being treated stereoscopically with good or bad results by using surgical, radiological or chemotherapeutic methods. In surgery, the surgical resection, tumor ablation (cryosurgery, ethanol ablation), embolization, and organs transplantation are carried out to treat the neoplasm. For radiotherapy high-energy rays are used to kill the cancer cells, Radio-sensitization, Radio frequency ablation used to assure the treatment. n immune therapy certain methods and drugs are used to boost the patient immune system (1). Restoring of tumor suppresser gene P53 might suppress tumor growth and cause "programmed cell death" of cancer cell (2)

Chemotherapeutical agents are used extensively in cancer treatment. Which, besides producing cure, exert deleterious effects on the body metabolism and bring structural and physiological changes in vital organs of the body. These drugs can damage the blood producing cells of bone marrow and patient may have low blood count resulting in increased chance of fatigue or shortage of breath (due to lower RBCs count), (3)

There are several types and stages of chemotherapy used to treat cancer i.e. induction therapy, consolidation therapy, intensification therapy, maintenance therapy, adjuvant therapy, palliative therapy, and chemo-preventive therapy (16). In this study, the anemic syndromes (toxicities) produced by Vinorelbine alone and vinorelbine based combinations (Vinorelbine/ Doxorubicin and Vinorelbine and Cisplatin) were compared. The clinical parameters i.e. erythrocytes count, hematocrit value, hemoglobin concentration, MCV, MCH, and MCHC were investigated pre & post chemotherapy to evaluate the therapeutical credibility of treatment protocol.

Materials and Methods

This research study was conducted at Shaukat Khanum Memorial Cancer Hospital & Research Center, M.A Johar Town, Lahore, Pakistan to investigate the changes in RBC's profiles of adult cancer patients with Non small cell lung cancer, metastatic breast cancer, and of cervix, being treated with Vinorelbine and Vinorelbine based combinations.

Study parameter

The cancer diagnosed patients, registered in SKMCH&RC and on treatment protocol of vinorelbine as part of their chemotherapy were investigated for alterations in RBC's profile; total erythrocyte count, hematocrit value, hemoglobin conc., mean corpuscular volume, mean hemoglobin conc. and mean corpuscular hemoglobin conc.

Study Design

A total 60 cancer patients irrespective of their age, sex, statues and occupation selected from out patient department (OPD), and wards of hospitals. These patients were then divided into two groups. Group-1 comprised of forty five (45) cancer patients taking vinorelbine as single therapy and Group-2 comprised of fifteen (15) cancer patients but on treatment protocol of vinorelbine based combinations i.e. Vinorelbine/Cisplatin vinorelbine/Doxorubicin. The clinical tests for alterations in erythrocytes count, hematocrit value, hemoglobin concentration, MCV, MCH, and MCHC were performed by an automatic computerized Auto-analyzer in the Pathology Laboratory of hospital.

The blood samples were drawn from brachial veins; 3 ml of blood was taken in 5c.c disposal syringe and then pushed in to C.B.C (complete blood count) vial, containing 20wro EDTA anti-coagulant. This vial was distinguished from other sample vials by its lavender top colored cap.

Chemical and Reagents

The materials, chemicals and instruments used comprised of 5 ml disposable syringes; complete blood count (CBCs) vial, normal saline (0.9% sodium chloride), ½ normal saline (0.45% sodium chloride), 5% dextrose (glucose) in steriled water, non-pyrogenic IV infusion (Otsuka), anticancer drugs –**Vinorelbine (Navelbine):** 10mg/ml and 50mg/5ml injection solution in vial, manufactured by Pierre Fabre Oncologic Laboratories, France, **Doxorubicin** hydrochloride USP (Deldoxin): 2mg/ml injection solution manufactured by Pharmacia & Upjohn (Perth) limited, Bently, Australia. **Cisplatin** (Cisplatinum): vials of 10mg/20ml, 25mg/50ml and 50mg/100ml Cisplatin Laboratories, Austria, **Auto-analyzer** (or CBC-Analyzer) Technicon 113, of Byer Laboratories USA.

Preparations of Standard Regimen of Chemotherapeutical Agents

Vinorelbine a mitotic spindle poison (antineoplastic) is available as 10mg/ml or Vinorelbine 50mg/ml.The Navelbine 10mg/ml injection solution in vial contains Vinorelbine ditartate 1385mg quantity corresponding to Vinorelbine (base) 1000 mg with water for injection sufficient quantity to make one full vial and Navelbine 50 mg/5ml injection solution in vial contain Vinorelbine ditartate 6925mg quantity corresponding to Vinorelbine (base) 5000 mg with water for injection sufficient quantity to make one full vial (4). The dose and protocol of Vinorelbine was as to administer 25 mg/m2 on day 1, weekly 4, i/v, with 045% sodium chloride or 5% glucose solution as diluents and delivered over IVP (15). The injected dose was diluted in normal saline solution (i.e. 125 ml) and infused over a short period -15 to 20 minutes (5). The administration was followed by a vein wash out using isotonic solution (6). In combination chemotherapy, the dose and frequency of administration was decided taking in to account stage and morphology of the neoplasm patient's condition and respective dose and protocol regimes (6).

In combination form the dose of Vinorelbine was as to administer 20 mg/m2 on day 1, 8 I/V with diluent day 5 ½ NS and delivered over IVP. The Doxorubicin was given as 50 mg/m2 on day 1 only as I/V with diluent 0.9% Sodium Chloride or 5% Glucose solution (repeated Q 3 weeks) (7), Doxorubicin Hydrochloride injection administered intravenously, keeping in view to reduce the chance of local reactions like urticaria and erythematous streaking. The dose schedule was 50mg/m2 body surface area, given as single intravenous injection at 21st day interval (6)

Doxorubicin was administered slowly in to tubing of freely running infusion of Sodium Chloride 0.9% or Glucose 5%. (8).

The Cisplatin is platinum derivative cytotoxic drug (6) and is available as 2ml vial containing 1mg Cisplatin as active ingredient. It is administered intra-venously as 40mg/m2 on day 1 only with the diluent of day 5 ½ NS and delivered over IVP.

The Cisplatin administered intravenously with 500 c.c. normal saline diluent at the dose rate for adults and children 40mg/m2 on day 1 of chemotherapy course. It was delivered over 2 hours. The Vinorelbine was administered as 20mg/m2 on day 1, 8 , I/V with Diluent day 5 ½ NS and delivered over IVP (intravenous push)

For breast cancer the Vinorelbine single therapy (5) and Vinorelbine / Doxorubicin combination therapy (9) where applied , for combination therapy (10) where used vial for cervix cancer the Vinorelbine /Cisplatin treatment was given to the patients. There was a criteria established to approach the patients having required characteristics i.e. the patients with definitive diagnosis of cancer, patients had not previous history of a severe systemic disease, especially relating to the hemic system, the patient with normal base line blood profile.

Laboratory analysis

The blood samples were drawn from brachial vein. 3ml of the blood was collected in 5cc disposable syringe and then pushed into CBC vial, containing 20ul EDTA anticoagulant. This vial was distinguished from other sample by lavender top colored cap. This autoanalyzer mad to suck the sample manually and the results were displayed on screen. The autoanalyzer validated and standardized before using to perform the tests.

Data Interpretation and Analysis

The data collected is manipulated and analyzed statistically to explore some clinically important findings.

Result and Discussion:

The mean values of Erythrocyte counts when compared over time there was a significant difference observed in Group-1 only (table 1). When values observed pretreatment were compared with those at week-4, significant differences were observed in both of the groups (table 2). While in an independent comparison of the mean values for two groups at every week, the differences were obtained at week-2 and week-3 table 1, 2 & 3 (table 3). These findings are supported by the work of Henry & Tretton, et al., (11), Gasparini, et al., (12), Fumoleau, et al., (13), who found the significant anemia in the cancer patients treated with the Vinorelbine as alone and combination with other cytotoxic drugs.

When the mean values of hematocrit compared overtime showed significant differences, Group-1 ($p<0.0001$) and in Group-II (P, 0.001) (table 1). The same significant differences were observed when values pretreatment were compared with those at week-4 in groups (table 2). While in an independent comparison of the mean values for two groups at every week, there were insignificant differences observed during all of the four weeks (table 3). These findings significantly correlate with the work of Dorr et. al., (4), who found the anemia in 2% of patients treated in Phase II studies with Vinorelbine. Gasparini, et al., (12), band Fumoleau, et al., (13), also found the significant anemia in cancer patients.

The mean values of hemoglobin when compared overtime, there was a significant difference observed in Group-II only (table 1). The significant differences were also observed when pretreatment values were compared with those at week-4 in both of the groups (table 2).

While in an independent comparison of the mean values for two groups at every week, there were insignificant differences obtained at all of the four weeks (table 3). The findings of this study are in line with the work of Henry & Tretton et al., (11), Gasparini, et al., (12) and Fumoleau, et al., (13), who found the significant anemia in cancer patient, treated with the Vinorelbine as alone and combination with other cytotoxic drugs

Table 1. Comparison of P values* of cancer patients on treatment protocol of Vinorelbine (Group-I), Vinorelbine based combination (Group-II) and overall (60) patients.

Study Parameter	G-1	G-2	Overall
Mean SEM± Erythrocyte count (10^6) Per uL	0.001	0.001	0.001
Mean SEM± Hematocrit value %age	0.0001	0.001	0.001
Mean SEM± Hemoglobin conc. g/dL	0.117	0.001	0.011
Mean SEM± MCH uugm (picogram)	0.210	0.645	0.027
Mean SEM± MCV cubic micron	0.606	0.774	0.469
Mean SEM± MCHC %age	0.417	0.449	0.358

Table 2. 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

Study Parameter	P value W0	P value W1	P value W2	P value W3	P value W4
Mean SEM± Erythrocyte count (10^6) Per uL	0.638	0.644	0.234	0.162	0.782
Mean SEM± Hematocrit value %age	0.852	0.746	0.251	0.253	0.609
Mean SEM± Hemoglobin conc. g/dL	0.474	0.438	0.210	0.590	0.258
Mean SEM± MCH uugm (picogram)	0.758	0.419	0.154	0.516	0.175
Mean SEM± MCV cubic micron	0.429	0.884	0.524	0.548	0.812
Mean SEM± MCHC %age	0.729	0.108	0.887	0.470	0.749

Table 3. 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)

Study Parameter	Group-I	Group-II
Mean SEM± Erythrocyte count (10^6) Per uL	0.004	0.017
Mean SEM± Hematocrit value %age	0.001	0.010
Mean SEM± Hemoglobin conc. g/dL	0.001	0.003
Mean SEM± MCH uugm (picogram)	0.029	0.524
Mean SEM± MCV cubic micron	0.434	0.606
Mean SEM± MCHC %age	0.160	0.450

The mean values of MCH when compared overtime, there was insignificant differences observed in both of the groups (table 1). The significant difference ($P<0.029$) was observed when values pretreatment were compared with those at wek-4 in Group-1 only (table 2). While in an independent comparison of the mean values for two groups at every week, there were insignificant differences obtained during all of the four weeks (table 3). The mean values of MCV when compared overtime, there were insignificant differences observed in both of the Groups (table 1). The mean values of MCHC when compared overtime, there were insignificant differences observed for both of the groups (table 1). When the values of pretreatment were compared with those at week-4, there were insignificant differences observed in for both of the groups (table 2). While in an independent comparison of the mean values for two groups at every week, there were insignificant differences obtained during all of the four weeks (table 3). Similarly there were insignificant differences observed when values pretreatment were compared with those at week-4. These findings are in line with the work of Romero, et al., (14), Fumoleau, et al (13), and Gasparini, et al (12), who found the Myelosuppression, and decreasing of the blood cell count by the treatment with Vinorelbine alone and Vinorelbine based combinations in different cancerous patients,

By the overall comparison of mean values overtime, there were significant toxicities of erythrocyte & hematocrit value were observed in the patient on treatment protocol of Vinorelbine alone and toxicities of erythrocytes, hematocrit value, & hemoglobin concentration were observed in the patients on treatment protocol of Vinorelbine based combinations. By an independent comparison of mean values of two groups at every week, there were no significantly toxicities observed in the patients on the treatment protocol of vinorelbine based combinations. When the mean values observed before therapy were compared with that of week-4, there significant decreased noted in erythrocyte count, hematocrit value and Hb concentration in the patients on treatment protocol of Vinorelbine alone, and erythrocyte count, hematocrit value and hemoglobin concentration in the patient on treatment protocol of Vinorelbine based combinations.

It can now be inferred from this study that, there is insignificant difference in the overall alteration in RBC's profile induced by both of the chemotherapy protocols. The clinical oncologist, consultant physician and pharmacist, therefore can probably select either of the chemotherapy protocol. It follows that therapeutic efficacy probably should constitute the overriding consideration in treating a particular neoplasm.

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