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Original Research Article

STUDY OF CORRELATION IN TUMOR MARKERS STATUS AND VITAMIN B_{12} DURING CHEMOTHERAPY IN CANCER PATIENTS

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ABSTRACT

Background: The study was carried out to find out alteration and correlation in the behavior of tumor markers of interest (CEA, AFP, CA-125, TSH &Vitamin B_{12}) in the cancer patients (n=25), who were picked randomly for the study, irrespective of the type, particular stage, and involvement of a specific organ. **Materials and methods:** The studied tumor markers were (CEA, AFP, TSH, CA-125 & Vitamin B_{12}) evaluated before chemotherapy (which was being done through the drug of choice for the specific type of cancer), after 1st cycle & after 2nd cycle (post-treatment) of chemotherapy. The tumor markers were estimated by chemiluminescent immunometric assays, their values at three different stages were compared and evaluated statistically (by 'p' & 't' values), Vitamin B_{12} was correlated with all other four tumor markers and statistical evaluations are done to calculate 'p', 't '& 'r' values. **Results:** All tumor markers besides Vitamin B_{12} followed a decreasing pattern from pretreatment to till 2nd cycle of chemotherapy (CEA=9.5>5.0>2.6; AFP=7.3>4.2>2.7; TSH=5.5>3.6>3.0; CA-125=185>93>45.5 & Vitamin B_{12}=292<662<1262). Before chemotherapy , a negative correlation was found between vitamin B_{12} and each of the tumor markers (CEA r= -0.44;p< 0.019: AFP r= -0.25;p<0.20: TSH r=-0.44;p,0.019:CA-125 r= -.0108;p<0.5).After 2nd cycle of chemotherapy only CEA was found negatively correlated with vitamin B_{12} significantly(r=-0.108;p<0.16),while the correlation with other markers altered in positive correlation (AFP r=0.12;p<0.54 : TSH r=0.08;p<0.66 : CA-125 r=0.42;p<0.02). **Conclusion:** Such findings of change in correlation pattern, suggest the role of Vitamin B_{12} similar to a potent tumor marker as well as its synchronizing pattern with other markers. It may help in deciding the direction of the treatment for betterment, in spite of the fact that it is a micronutrient. Dramatically, its (Vitamin B_{12}) correlation alters with all tumor markers leaving CEA as treatment proceeds, i.e. different from initial stages. This alteration can define the protective measures taken by the stressed normal cells undergoing the process of chemotherapy along with the destruction of cancer cells, however, they try to achieve the homeostasis as soon as possible.

Key Words: Vitamin B, Tumor Markers, Chemotherapy Correlation, Homeostasis, etc.

INTRODUCTION

It is well known that patients with malignant disease frequently use dietary supplements, but due to their variation in body, the effects of these agents with regard to chemotherapy and tumor markers are unclear **(1)**. Most of the tumor markers like AFP, CEA, Vitamin B_{12}, TSH, and many more, function for the diagnosis of more than one type of cancer. So, their importance lies much in their variation during diagnosis, treatment & prognosis more than the type of cancer and tissue/organ they originate from. Therefore, the authors investigated the influence on and variation of vitamin B_{12} during chemotherapy in relation to variation in tumor marker status in various types of cancers.

Although studies on the significance of elevated vitamin B_{12} levels in cancer patients are limited, an

association has recently been reported **(2,3)**. Vitamin B_{12} is being studied as a nonspecific tumor marker, as well as an indicator of survival time **(4)** and its raised serum levels are associated with the higher mortality rate in hepatocellular carcinoma patients**(5)**.

Tumor markers are proteins specially glycoproteins, present in the blood, body fluids, tumors, and other tissues **(6,7,8)**. Most of the common tumor markers like β-HCG, CEA, CA-125, AFP, and TSH were discovered after the development of monoclonal antibodies**(9)**. Recently, the new tumor/cancer detection methods are also being developed based on the variations in patterns and modes of gene expressions, mutations, or the changes brought about by tumor in DNA **(10)**.

Cancer treatment is a combination of palliative care and specific therapies like chemotherapy, immunotherapy, radiotherapy, gene therapy, and hormone therapies **(11)**. Drug specific chemotherapies are the choicest ones, as they can be used to treat spread and metastasized cancers because the medicines travel throughout the entire body **(12)**. Moreover, chemotherapy targets rapidly dividing cells by damaging their DNA and protein in both, cancer cells and normal cells, where normal cells are recovered but cancer cells are destructed **(13,14)**.

Being a micronutrient as well as its response towards the carcinogenesis, vitamin B_{12} is included in diagnostic markers for various cancers **(15)**. The detectable presence of Vitamin B_{12} and other tumor markers with specific pattern decides the presence of certain cancers also **(16)**.

In the present study, the effort has been done to evaluate the variation and correlation, if, any, between various tumor markers and B_{12} levels of the cancer patients who were going under chemotherapeutic cycles according to the stage and chemotherapeutic cycle.

MATERIALS AND METHODS

The entire study was carried out in the Department of Biochemistry in SMS Medical College and attached hospitals. Samples were collected from 25 indoor cancer patients in the oncology department, irrespective of the organ involved and the type of cancer. The basis of the study was purely biochemical and no animals were harmed for the study. The demographic criteria were also taken into account. The study comprised of pretreatment stage and two cycles of 21 days i.e. divided into three stages, Pretreatment (before 1st cycle), after1st cycle, and post-treatment (after 2nd cycle).

Standard serological methodology **(17,18)** was used as required. In the study, only blood/serum parameters were estimated. All samples were calculated in different stages of cancer at a short duration. Blood Samples (5-7 ml) were collected in dry plain vials for serum assays. Storage required -20 ℃ for longer periods and 2-8 ℃ was required for 7 days storage. The serum was separated and centrifuged. The serum was used for assays. All general Biochemical Parameters were analyzed on Olympus AU-400, AU-680. Tumor markers were analyzed on Immulite 2000 **(19, 20)**.

CEA, AFP, TSH, CA-125, and Vitamin B_{12} were analyzed through a solid phase two-site sequential chemiluminescent immunometric assay **(21)**. Chemical Kit and components were matched set for all tumor markers. Provided kits required barcodes. Incubation time varied 1hr 60 min to 3 hr 30 mins. Evaluations of results were based on the reference range of the kits based on observational population studies carried out. Medians and 95th Percentile for relevant subgroups were provided, where percentiles were determined non-parametrically **(19,20,21)**. Samples were assayed under various dilutions.

Calibration range and analytical sensitivity for CEA was up to 550ng/ml and 0.15ng/ml and high dose hook effect was none up to 250000ng/ml, for AFP calibration range was 300 IU/ml and analytical sensitivity was 0.2IU/ML, no high dose effect up to 53400IU/ml. There was a negligible impact of bilirubin and hemolysis. The antibody was highly specific for TSH for that the calibration range was up to 75Uiu/ml with an analytical sensitivity of .004 u IU/ml, high dose hook effect none up to 14000 uIU/ml. In Immulite 2000 Vitamin B_{12} assay is a solid phase, competitive chemiluminescent enzyme assay involving an automated alkaline denaturation procedure, using alkaline phosphatase labeled anti-hog intrinsic factor, incubation cycles were of 3hr30mins. CA-125 was also two-site chemiluminescent immunometric assay, had calibration range up to 500U/ml, analytical sensitivity 1U/ml, and none high dose hook effect up to 80000U/ml.

RESULTS

The study was carried out on 25 subjects who were fitting to the major criteria of the study, irrespective of the type of cancer and involvement of a particular organ. The study comprised of pretreatment stage

and two cycles of 21 days i.e. divided into three stages, Pretreatment (before 1st cycle), after the 1st cycle, and post-treatment (after 2nd cycle).

Table 1 shows the normal range of tumor markers and vitamin B_{12}. Table 2 shows summarized average values of pre, 1st, and 2nd cycle (i.e.also post-treatment/end cycle values) stage. Tables 3 (comparison between 1st and 2nd cycle values), 4 (comparison between Pre & 2nd cycle) & 5 (comparison between Pre & 1st cycle values) show comparative statistical evaluations as 'p' and 't' between three stages(pre ,1st & 2nd).Table 6 shows the correlation of Vitamin B_{12} with other tumor markers in at pre-treatment stage i.e. before 1st cycle starting of chemotherapy mentioned as the pre-treatment correlation. Table 7 shows the correlation of vitamin B_{12} in after 2nd cycle of chemotherapy i.e. post-treatment correlation. Plots are drawn (plots1 to 5) to show the comparison of each tumor marker at pretreatment, after 1st cycle of chemotherapy and after the 2nd cycle of chemotherapy.

Table-1

Normal Range of All Parameters (19)

S.No.	Parameters	Normal Range
1.	CEA	<2.5 ng/ml in an adult non-smoker and <5.0 ng/ml in a smoker
2.	AFP	less than 10 μg/L
3.	TSH	0.4 – 4.0 uIU/ml
4.	CA-125	Up to 21 U/ml
5.	Vit-B_{12}	193-982 pg/ml

Table-2

A Summarized Table for Mean and S.D.

S. No.	Parameters	Stage	No. of Case	Mean± S.D.
1.	CEA	Pre	25	9.5048±7.8878
		1^{st}	25	5.0736±3.67102
		2^{nd}	25	2.616±1.76252
2.	AFP	Pre	25	7.3488±5.41146
		1^{st}	25	4.2108±2.87541
		2^{nd}	25	2.7117±2.2649
3.	TSH	Pre	25	5.5552±3.7539
		1^{st}	25	3.6062±2.43683
		2^{nd}	25	3.0740±2.00812
4.	CA-125	Pre	25	185.74±205.3625
		1^{st}	25	93.044±113.2561
		2^{nd}	25	45.541±41.26052
5.	Vit-B_{12}	Pre	25	292.12±146.5194
		1^{st}	25	662.28±172.6571
		2^{nd}	25	1262.12±461.9759

Table-3

A Comparative Table between 1st Cycle and 2nd Cycle

S.No.	Parameters	Stage	Mean ± S.D.	't'–value	'p'–value
1.	CEA	1st	5.0736 ± 3.67102	0.002035	0.998704
		2nd	2.616 ± 1.76252		
2.	AFP	1st	4.2108 ± 2.87541	0.023038	0.985336
		2nd	2.7117 ± 2.2649		
3.	TSH	1st	3.6062 ± 2.43683	0.201748	0.873264
		2nd	3.0740 ± 2.00812		
4.	CA-125	1st	93.044 ± 113.25609	0.055147	0.964928
		2nd	45.541 ± 41.26052		
5.	Vit-B_{12}	1st	662.28 ± 172.65706	9.4188E-08	1
		2nd	1262.12±461.97595		

Table-4

A Comparative Table between Pre-Treatment and 2nd Cycle

S.No.	Parameters	Stage	Mean ± S.D.	't'–value	'p'–value
1.	CEA	Pre	9.5048 ± 7.88786	4.1746E-05	0.99996999
		2nd	2.616 ± 1.76252		
2.	AFP	Pre	7.3488 ± 5.41146	0.000127	0.999919
		2nd	2.7117 ± 2.2649		
3.	TSH	Pre	5.5552 ± 3.7539	0.002702	0.99828
		2nd	3.0740 ± 2.00812		
4.	CA-125	Pre	185.74 ± 205.3625	0.001422	0.999095
		2nd	45.541 ± 41.26052		
5.	Vit-B_{12}	Pre	292.12 ± 146.5194	1.23722E-13	1
		2nd	1262.12±461.97595		

Table-5

A Comparative Table between Pre-Treatment and 1st Cycle

S.No.	Parameters	Stage	Mean ± S.D.	't'–value	'p'–value
1.	CEA	Pre	9.5048 ± 7.88786	0.00707028	0.99549899
		1st	5.0736 ± 3.67102		
2.	AFP	Pre	7.3488 ± 5.41146	0.006828	0.995653
		1st	4.2108 ± 2.87541		
3.	TSH	Pre	5.5552 ± 3.7539	0.0172	0.989051
		1st	3.6062 ± 2.43683		
4.	CA-125	Pre	185.74 ± 205.3625	0.02696	0.982841
		1st	93.044±113.25609		
5.	Vit-B_{12}	Pre	292.12 ± 146.5194	6.03449E-11	1
		1st	662.28 ± 172.65706		

Table-6

Correlation between Vitamin B_{12} and Other Parameters at the pretreatment stage (Before 1st cycle)

S.No.	Vit-B_{12} and Parameters	No. of Case	'r'–value	'p'–value
1.	CEA	25	–0.05263	0.7943
2.	AFP	25	–0.25043	0.2077
3.	TSH	25	–0.44823	0.0190
4.	CA-125	25	–0.10849	0.5901

Table-7

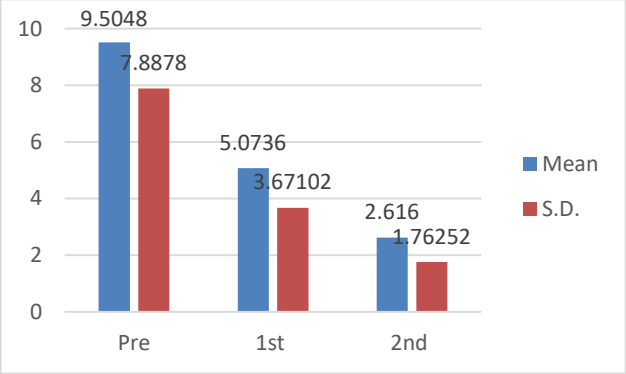
Correlation between Vitamin B_{12} and Other Parameters at post-treatment

Stage (After 2nd cycle)

S.No.	Vit-B_{12} and Parameters	No. of Case	'r'–value	'p'–value
1.	CEA	25	–0.27507	0.1649
2.	AFP	25	0.121456	0.5462
3.	TSH	25	0.086973	0.6662
4.	CA-125	25	0.427557	0.0261

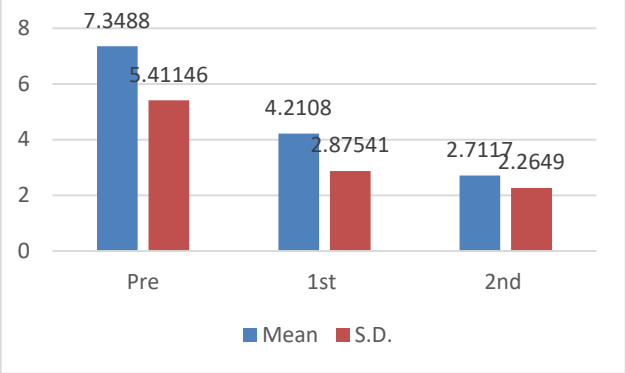
Plot – 1

Comparison of CEA in Pre and Post Treatment



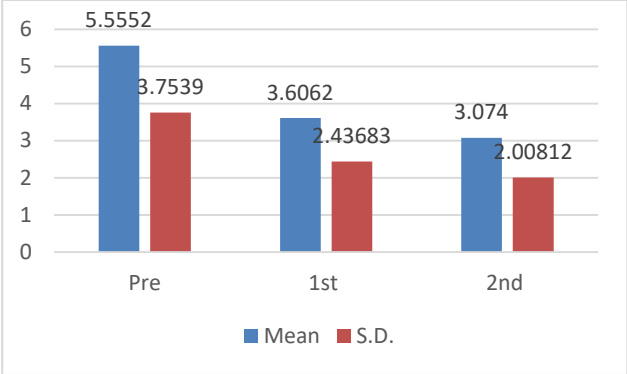
Plot – 2

Comparison of AFP in Pre and Post Treatment



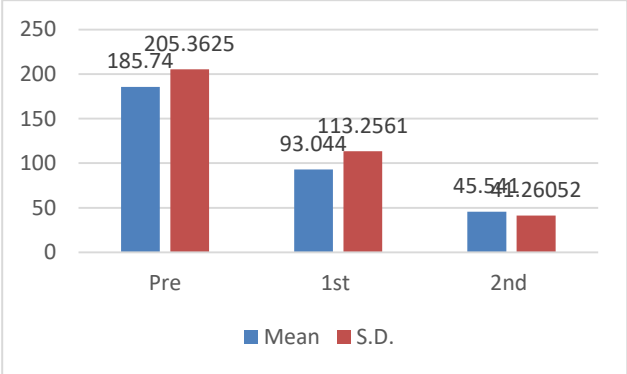
Plot – 3

Comparison of TSH in Pre and Post Treatment



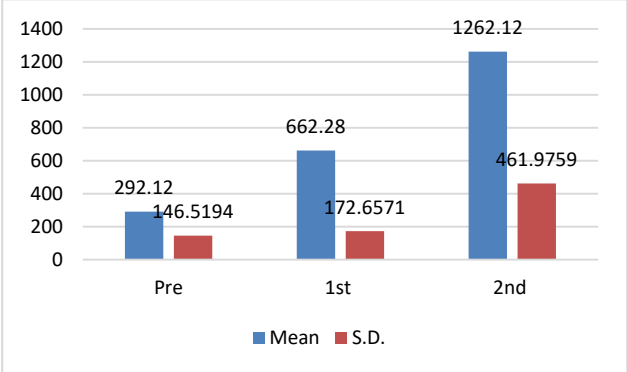
Plot – 4

Comparison of CA-125 in Pre and Post Treatment



Plot – 5

Comparison of Vitamin B_{12} in Pre and Post Treatment



DISCUSSION

Assayed tumor markers were CEA, AFP, TSH, CA-125, and Vitamin B_{12}. The effects of chemotherapeutic drugs on tumor markers level may happen when people have therapy for a long time (22).

CEA was estimated before and during the chemotherapy, the average CEA value at the pre-treatment stage was 9.50 ± 7.88 in comparison to post-treatment values of 1st cycle 5.07 ± 3.67, and 2nd cycle 2.61 ± 1.76. The difference was poorly significant ($p<0.99$). It was found that the values of CEA were decreased during treatment, and when correlated with vitamin B12 between pre-treatment and 2nd cycle (table 6, 7), a negative correlation was found, contrary to the other markers. These findings could be explained based on the incidence of cell mass damage and the type of cancer and involvement of the liver **(22,23)** as well as signaling the asymptomatic reoccurrence. The CEA and other markers are shown in table 5, more rapid rises in CEA are seen with hepatic metastases than localized recurrence and respectable localized tumors. Several studies have suggested a correlation between the rate of rising in CEA and the presence or probability of hepatic metastases as it induces cytokine expression in Kuffer cells **(24)**.

AFP level in the pre-treatment cycle was 7.35±5.41 and 4.21 ± 2.87 in the first cycle and 2.71 ± 2.26 in the second cycle. This difference in decreasing values was significant by a $p<0.9$ (table 2, plot 2). It has been reported that AFP levels frequently rise during disease progression and fall during disease remission **(25)**.

TSH level was 5.55 ± 3.75 as measured before chemotherapy, then it was 3.60 ± 2.44 after the first cycle and 3.07 ± 2.00 after the second cycle. A decreasing order was found in pre and post-chemotherapy cycles. The decrease in TSH level in the study is just similar to secondary or tertiary hypothyroidism where it is secondary to the lesions in pituitary and hypothalamic regions, but here it may be secondary to the impact of carcinogenesis **(26)**. On the contrary, in primary hypothyroidism, where there is impaired production of thyroid hormones, the TSH level is typically highly elevated.

The approximate level of CA-125 was 185.74 ± 205.36 in pre-treatment and 93.04 ± 113.25 was after the first chemotherapeutic cycle and 5.54 ± 41.26 after the second cycle. The values are decreasing and moderately significant.

Vitamin B_{12}, the major correlative parameter of the study was found significantly elevated after starting chemotherapy i.e. 662.28 ± 172.65 after the first cycle and 1262.12 ± 461.97 after the second chemotherapeutic cycle than the 292.12 ± 146.51 value at pre-treatment cycle. The vitamin B_{12} values are poorly significant ($p<1$) when two phases /cycles were compared.

All other tumor markers were correlated with Vitamin B_{12}. Vitamin B_{12} has got the attention of being diverse i.e. an essential micronutrient and also as a tumor marker to diagnose some cancers. Table 6, 7 shows a correlation of Vitamin B_{12} with other tumor markers in pretreatment and after 2nd cycle. The involvement of Vitamin B_{12} in defining cancers and their prognosis by reducing cell mass damage in correlation with altered values of tumor markers is studied by some authors **(27)**. Common causes of high vitamin B_{12} levels include liver disease, myeloproliferative disease **(28)**. Similarly here, it may be due to the altered behavior of normal stressed cells during chemotherapy to compensate for the changing environment of the body. Some previous studies provide ideas about the relation of Vitamin B_{12} and folic acid **(29)** and its impact in children in some cancers **(30)** but the studies about the correlation between tumor markers status and vitamin B_{12} are limited.

A negative correlation of all tumor markers with vitamin B_{12} was found initially before or at starting the chemotherapy (table-6). As the values were compared/correlated between the pretreatment stage and 2nd cycle (post-treatment) a negative correlation was established with CEA and positive correlation values with AFP, TSH, and CA-125 (table 7). This change in correlation pattern indicates the altered behaviors of tumor markers in altered conditions and the environment.

So, the effect of alteration in the status of tumor markers during chemotherapeutic cycles can explain the involvement of other bodily factors, who initially, resist the change, and then afterward compensate by collaborating with the micronutrient Vitamin B_{12}, who is already involved in basic metabolic mechanisms and still functions as a tumor marker, especially in challenging conditions like cancer and chemotherapy. It looks that the harmful effect on the normal cell can be measured by the capacity of the body to take the challenge to utilize the higher availability of Vitamin B_{12}, who works cumulatively with the metabolic mechanisms of the body because the body tries to bear and manage the hazardous effects of the chemotherapy.

On the other hand, the decreased level of tumor markers observed during the study reflects the decrease in tumor cell mass and shows the effectiveness of the chemotherapy. Despite that, on the contrary, this may affect adversely the normal

cells, where Vitamin B12 is increasing in response to underutilization or supplementation. Hence, it looks that it shares a compensatory mechanism with its routine metabolic functions during chemotherapy.

CONCLUSION

Sometimes evaluating tumor size is impossible in diffusely spreading cancers and a safe and non-invasive way like estimating the tumor marker levels seems better to evaluate the diagnosis and prognosis of the tumors.

Moreover, the side effects of chemotherapy may also occur as treatment approaches towards the end or maybe even during treatment. Depending on the type of chemotherapy received, the liver, kidney, and other organs may be affected and side effects may be short term and reversible. However, but still, the patients must be monitored closely and be examined routinely for blood chemistry and other markers.

In the present study, different types of cancer patients were involved because many markers like AFP, CEA, CA-125, TSH & Vitamin $B_{12,}$ etc. define more than one type of cancer. Vitamin B_{12} was found to increase subsequently. A negative correlation with vitamin B_{12} with other markers was found at initial stages but after treatment, only with CEA it remained negatively and dramatically changed to a positive correlation with the rest of other tumor markers i.e. AFP, CA-125, and TSH.

The variation of different parameters in different patients depends on the variation of drugs and particularly a subject's dietary and drug regularizing plans as well as the stage of cancer and size of tumors, and lastly, the ability to fight the disease.

These results were not highly significant statistically but were sufficiently capable to define an average effect of chemotherapeutic drugs to lead the direction of prognosis by variation in tumor markers during three short cycles of the study.

Usually, the reason to give time between chemotherapeutic cycles is to give time to normal cells to heal themselves. More importantly, designing the study in short cycles seemed helpful in deciding the most alarming days of the treatment i.e. from the first cycle to the second cycle there were more significant alterations in values of the parameters which were noteworthy (see observation tables).

Here, a brief conclusion can be drawn that the body shows its compensatory mechanism towards any metabolic hazards, and chemotherapy is one of them. So, during the progression of chemotherapy, normal body cells who utilize vitamin B_{12} for various basic metabolic reactions, are also harmed and they try to homeostasis to normal metabolic states as soon as possible. The alteration of the correlation of vitamin B_{12} shown with tumor markers is one of the various ways among all defensive and compensatory mechanisms to overcome the stress of fighting with changed inner biochemical environments of the cell and body (due to the presence of foreign chemicals i.e. drugs, during chemotherapy.)

Henceforth, also the routine biochemical parameters like Vitamin B_{12} when correlated with other biomarkers can define the direction of the metabolic response of treatment, which is important to compensate if there is no known complication.

Moreover, if a negligible variation or insignificant alteration is noted in particular tumor markers, then their correlation pattern with some routine parameters like Vit B_{12} may also decide the prognostic outcome of the treatment during or after chemotherapy.

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