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CA125 in Non Hodgkin's Lymphoma and its association with severity of the disease

V. Lokanathan[1*], Garima Gupta[1], V.S. Ghalaut[1], P.S. Ghalaut[1], Dharambeer S. Mahor[1], Anju Mahor[2]

PT B.D. Sharma PGIMS Rohtak[1]

LHMC New Delhi[2]

*Corresponding Author : V . Lokanathan

Abstract

The objective of this study was to assess status of CA-125 in patients of Non Hodgkin's lymphoma as a diagnostic marker and to find out the relationship between the level of CA-125 and the stage of the disease and on the basis of International Prognostic index (IPI). For the study ,30 newly diagnosed patients of Non Hodgkin's Lymphoma were selected .Venous blood was collected from these patients and tested for CA-125 levels by using two-site sandwich immunoassay using direct chemiluminometric technology in ADVIA- CENTUAR CP. Age and sex matched controls were also selected and their CA-125 levels were also measured similarly. This study was conducted in the Department of Biochemistry in collaboration with the Department of Oncology, PGIMS, Rohtak between December 2013 to June 2014.Results obtained showed that CA-125 was found to be raised in all the patients; whereas the levels of CA-125 in controls were within normal range .The CA-125 levels in controls was 15±8 U/l. The CA-125 in Stage I and stage II patients was 577.17 ± 252.61 IU/l, that in Stage III and IV patients was 914.86 ± 95.743 IU/l. ,. All the results were found to be statistically significant ($p<0.05$). The levels of CA - 125 were highest in patients of hifh risk category as per IPI and lowest in low risk category. It was concluded that CA-125 was found to be uniformly raised in all patients and more so in patients with a more advanced stage of Non Hodgkin's Lymphoma. Thus CA-125 has a potential role as both a diagnostic and prognostic marker in Non Hodgkin's Lymphoma.

KEYWORDS : Non Hodgkin's lymphoma, CA 125, Stage, IPI

Introduction

Lymphoma, is described as proliferations of lymphoid cells arising as discrete tissue masses.[1] There is a worldwide epidemic of Non Hodgkin's Lymphoma that varies according to gender, age and geography. The rise in NHL has been faster in comparison to most of the malignancies. According to Bhopal registry, the incidence of Non- Hodgkin's lymphoma is 1.44 in 1000 females and 2.49 in 1000 males[2]. The prognosis of patients with non-Hodgkin's lymphoma is best assigned using the International Prognostic Index (IPI) (Annexure1). [3] It is a predictor of outcome in all subtypes of non-Hodgkin's lymphoma. Patients are assigned an IPI score based on the presence or absence of five adverse prognostic factors and may have none or all five of these adverse prognostic factors.[4]

CA-125 (cancer antigen 125 or carbohydrate antigen 125) also known as mucin 16 or MUC16 is a protein that in humans is encoded by the MUC16 gene. MUC16 is a member of the mucin family glycoproteins.[5] CA-125 has found application as a tumor marker or biomarker that may be elevated in the blood of some patients with specific types of cancers, or other benign conditions.[6]

In 1998, Lazzarino et al found that high serum CA-125 levels were found to be a reliable biologic marker for the staging and restaging of patients with lymphoma.[7] Bairey et al observed that Serum CA-125 levels at diagnosis had strong association

with event-free and overall survival, with the patients with increased levels having worse survival in NHL.[14] Wei et al observed that Serum CA-125 levels were associated with clinical stage, effusions, high serum LDH and beta2-microglobulin levels, and response to therapy in NHL.[8] Battle et al observed that CA-125 was associated with advanced stage, lung, pleural or gastrointestinal tract involvement in NHL.[9] In 2010 Gutierez et al found that patients with elevated serum CA-125 levels in NHL had significantly more adverse prognostic factors at diagnosis, higher relapse rates and worse survival.[10]

This study was done to find out association of CA-125 with NHL as very few previous studies had been undertaken on this in India. This also intended to demonstrate the relation of CA-125 with staging and with IPI score, hence try to find a diagnostic and prognostic role of CA-125 in NHL.

Material and Methods

The present study was conducted in the Department of Biochemistry, in collaboration with the Department of Medicine (Clinical Haematology Unit), in PT. B.D.SHARMA PGIMS, Rohtak from December 2013 to June 2014.

Inclusion criteria

Patients diagnosed with Non hodgkin's lymphoma in this institution. 30 patients confirmed with diagnosis of Non Hodgkin's Lymphoma and 30 age and sex matched controls were included in this study. A written consent was obtained from all the patients, participating in this study.

The diagnosis of patients of non Hodgkin's lymphomas was made by careful history and physical examination, complete haemogram, major organ function tests, lymph node biopsy and imaging studies of the chest and abdomen looking for pathologic lymphadenopathy, relevant immunochemistry and cytogenetic studies. CA-125 was done at the time of diagnosis.

5ml of venous blood sample was collected from patients at the time of diagnosis in a plain red capped evacuated vaccutainers under all aseptic precautions. Samples were processed within one hour of collection. Serum was separated by centrifugation (2000 rpm X 10 minutes) after clotting. Routine biochemistry was performed, and remaining serum was stored at -20˚C in deep freezer for CA-125 if not analysed immediately.

CA-125 levels was measured by two-site sandwich immunoassay using direct chemiluminometric technology, which uses two monoclonal mouse antibodies specific for CA-125. The tests were on ADVIA CENTAUR-CP .[11]

Statistical analysis

The data was analysed after compilation using various statistical methods viz. p-value, mean median, bar chart, t-test, ANOVA. Statistical analysis was done by SPSS software.

Results

We assessed 30 patients of NHL and 30 sex matched controls. We found that the mean of CA-125 in patients was 655.73 ± 267.23 IU/l, whereas the mean in controls was 15±4 IU/l. The results were put to a paired t test which showed high significance ; $p < 0.001$, as shown in table 1 and figure 1.

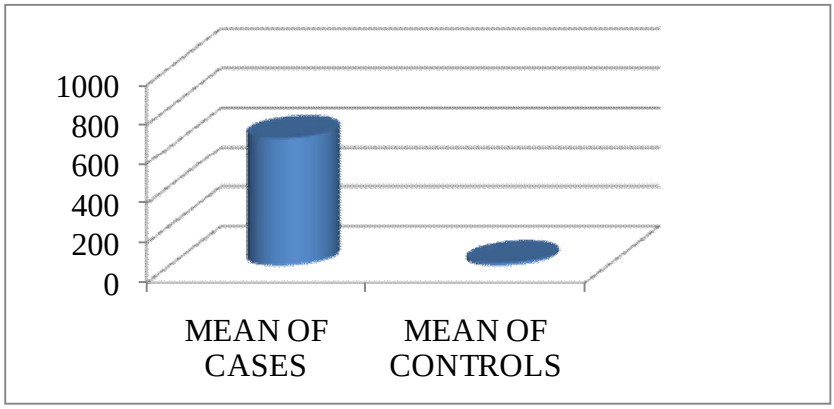

Figure 1 CA 125 in cases and controls, showing that CA 125 is significantly higher in cases of NHL than in controls

TABLE 1 Levels of CA 125 in cases of NHL and in controls

	MEAN (IU/l)	STANDARD DEVIATION
CASES OF NHL	655.73	267.23
CONTROLS	14.0	4.0

$p<0.001$

We divided the patients according to various stages of NHL, 14 were in stage I, 9 in stage II, 2 in stage III and 3 in stage IV as stated in table 2

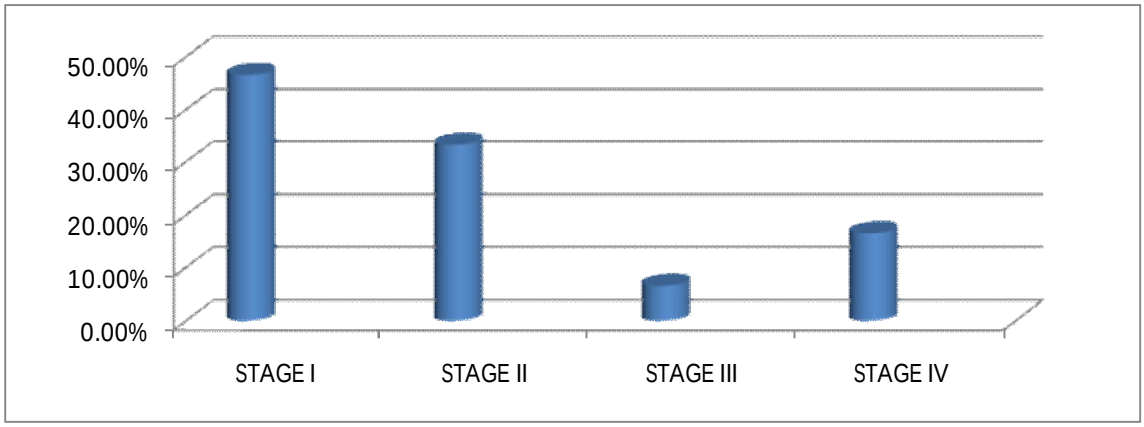

Figure 2 Distribution of patients according to stage of disease

It was found that the levels of CA 125 were significantly higher in patients in stage III and IV than in those in stage III and IV.($P<0.001$). The mean of CA125 in stages I and II being 577.17 ± 252.61 IU/l , while that in stages III and IV being 914.86 ± 95.743 IU/l., as shown in figure 3 and table 2.

TABLE 2 CA 125 in various stages of NHL

STAGE	N	Mean (IU/l)	Std. Deviation	p value
I +II	23	577.17	252.621	<0.001
III+ IV	7	914.86	95.743	

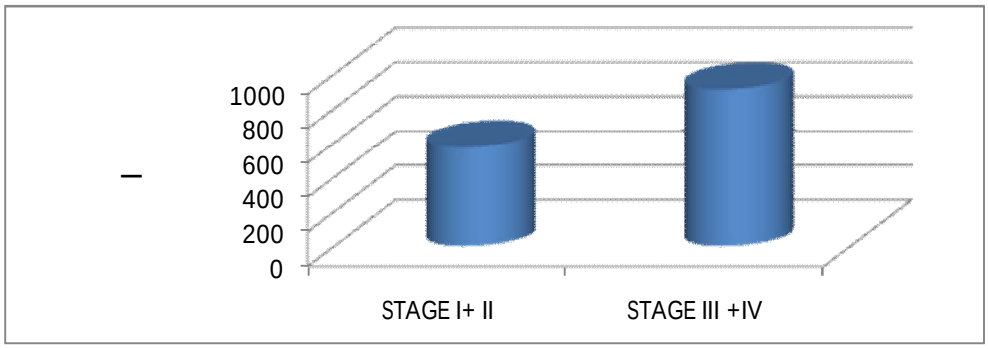

Figure 3 Levels of CA 125 in various stages of NHL

The patients were also divided according to International Prognostic index (IPI) and we found that 36.7 % patients were under high intermediate category, 33.3 % were in low intermediate risk category, 20% were in high risk and rest were in low risk, as shown in figure 4.

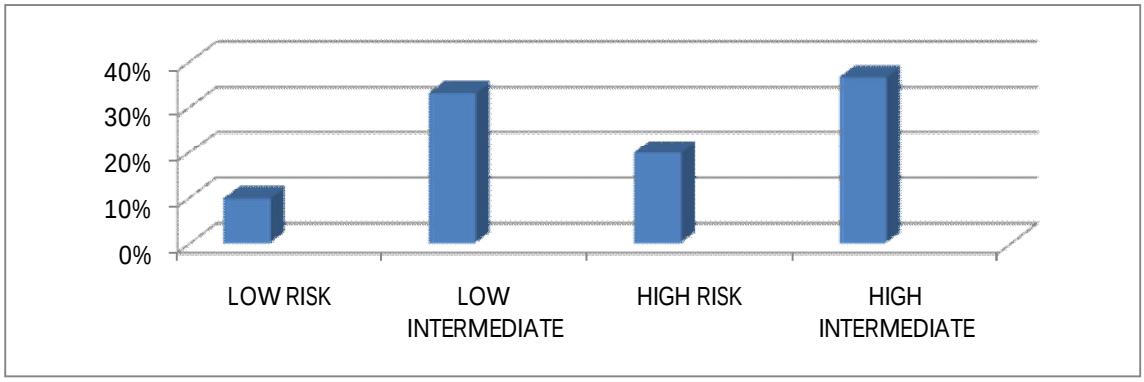

Figure 4 Distribution of patients according to International Prognotic Index (IPI)

It was found that the levels of CA 125 were highest in high risk patients , the mean being 935.83 ± 85.46 IU/l, and were lowest in low risk group , the mean being 138.33 ± 5.86 IU/l. An ANOVA test was done between CA-125 levels of patients divided into low risk, low intermediate risk, high intermediate and high risk. It was found that the levels in high risk were significantly higher than those in low risk, as shown in figure 5 and table 3.

TABLE 3 CA 125 levels on basis of International Prognostic Index

	N	Mean (IU/l)	Std. Deviation	Std. Error
Low Risk	3	138.33	5.859	3.383
Low Intermediate	10	609.80	190.073	60.106
High Risk	6	935.83	85.464	34.891
High Intermediate	11	686.45	200.967	60.594
Total	30	655.97	267.230	48.789

ANOVA TEST

	p value
Between Groups	<.001

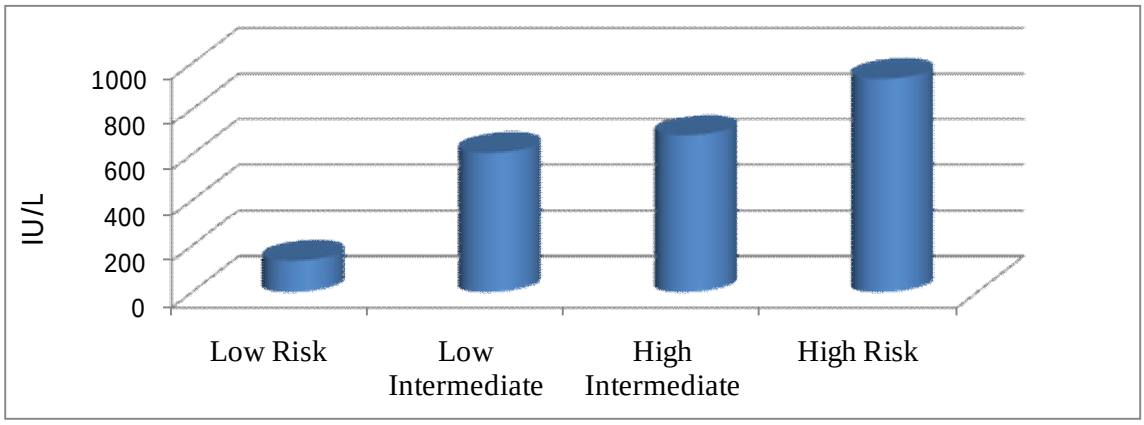

Figure 5 CA-125 levels on basis of International Prognostic Index

Discussion

In our study the CA 125 levels were found to be significantly high in newly diagnosed patients of NHL. This was similar to findings in Lazarrino et al which concluded that serum CA 125 is a reliable biologic marker for the staging and restaging of patients with lymphoma. Serial measurements are useful, in conjunction with other markers, for monitoring response to treatment.[7] The CA-125 levels were significantly higher in patients with Stage 3 and 4 disease rather than those with Stage 1 or 2 disease($p<0.001$). This is similar to studies by Ashour et al ($p<0.05$) and Bairey et al ($p=0.03$).[12]

After classifying patients on IPI, an ANOVA test was applied and it was found that CA-125 levels were significant highest in high risk , lesser in high intermediate and least in low risk ($p<0.001$). Bairey et al had observed that serum CA 125 levels at diagnosis had strong association with event-free and overall survival ($p = 0.01$ and 0.003, respectively), with the patients with increased levels having worse survival. In conclusion, CA 125 is not only a reliable marker for staging and assessing tumor activity in NHL, elevated levels are also predictive of decreased survival.

CA 125 is also thought to participate in cell-to-cell interactions that allow for the metastasis of tumor cells. This is supported by evidence showing that MUC16 binds selectively to mesothelin, a glycoprotein normally expressed by the mesothelial cells of the peritoneum (the lining of the abdominal cavity). MUC16 and mesothelin interactions are thought to provide the first step in tumor cell invasion of the peritoneum. Mesothelin has also been found to be expressed in several types of cancers including mesothelioma, ovarian cancer and squamous cell carcinoma. Since mesothelin is also expressed by tumor cells, MUC16 and mesothelial interactions may aid in the gathering of other tumor cells to the location of a metastasis, thus increasing the size of the metastasis.[13]

Conclusions

1. CA 125 may be a potential diagnostic marker in NHL as it is significantly raised in newly diagnosed patients of NHL.
2. CA 125 may be used as a tool to supplement others in stagings as its levels were significantly raised in stages III and IV in comparision to stages I and II
3. CA 125 may be used as a prognostic marker as CA 125 levels were significantly highest in patients of high risk group on basis of International Prognostic index (IPI).
4. Further studies are needed to substantiate these findings so that new markers of prognosis and diagnosis are able to develop in NHL to help reduce disease burden.

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