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Original article

CA 125 Levels in B Cell Non Hodgkin Lymphoma

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Abstract

Aim of the work: study the levels of CA 125 in patients with B-cell non-Hodgkin lymphoma and to evaluate its value as an index for the disease extent and response to treatment. **Methods:** forty two patients, including 22 male patients (52.4%) and 20 females (47.6%,) including various age groups ranging from 19 to 65 years, with histological diagnosis of B cell NHL were enrolled in this study whom were newly diagnosed and untreated. After documenting full medical history and clinical evaluation, investigations including bone marrow biopsy, CT scans, baseline haematology and biochemistry were done. Serum CA-125 levels were measured at diagnosis and after completion of 6 cycles of CHOP chemotherapy regimen. **RESULTS:** The studied patients including 35 patients (83.3%) with diffuse large B cell lymphoma, 5 patients (11.9%) with follicular lymphoma and 1 patient (2.4%) for each of nodal marginal zone lymphoma and small lymphocytic lymphoma. High pretreatment levels of CA 125 were associated with advanced stage, poor ECOG performance status, high LDH, bone marrow involvement ,presence of B symptoms and extranodal disease .CA-125 levels before and after treatment were higher in those with progressive disease followed by those with partial response and lowest levels were found in those with complete remission. **Conclusion**: Higher levels of CA-125 before treatment were associated with advanced, extranodal disease and poor response to chemotherapy.

Key words: CA125, Hodgkin lymphoma, B cell lymphoma

Introduction:

lymphomas are divided into 2 large groups of neoplasms, namely non-Hodgkin lymphoma and Hodgkin lymphoma. Specifying NHL it represent about 85% of all malignant lymphomas. The median age at diagnosis is the sixth decade of life, although Burkitt lymphoma and lymphoblastic lymphoma occur in younger patients. NHL includes B and T cell subtypes, each with distinct epidemiologies, etiologies, morphologic, immunophenotypic, genetic, clinical features and responses to therapy (1).

Caner antigen 125 is an antigenic determinant on a high–molecular-weight glycoprotein recognized by a monoclonal antibody (OC 125). The full-length CA 125 glycoprotein contains more than 11,000 amino acids in its proteinaceous core and has been termed Muc16 to reflect the mucin-like nature of the antigen and is now identified as a new member of the protein family of mucins. The precise function of the antigenic determinant is unknown but can be found in both benign and malignant tissues with normal level reaching 35 units/litre(2).

Up to 80% of women with ovarian carcinoma of epithelial origin have elevated serum CA 125 levels, with the frequency of elevation correlating with the clinically detected stage. The degree of elevation has also been shown to correlate with tumor burden and International Federation of Obstetrics and Gynecologic (FIGO) pathologic stage. However, owing to the lack of sensitivity and specificity, elevations in single or sequential CA 125 levels alone are not recommended for ovarian cancer screening or in the initial diagnosis of ovarian cancer. CA 125 levels may also be elevated in other malignancies, as well as in benign and physiologic conditions (3).

Higher levels of CA 125 were reported in patients with B cell non Hodgkin lymphoma having advanced disease, bulky tumours, effusion and/or extra-nodal extension not only that ,but also it was found that higher levels of this tumor marker was correlated with poor response to chemotherapy(4).

Patients and methods:

After obtaining approval by the Benha university Hospital Ethics Committee, and written informed consent from the patient, we studied 42 newly diagnosed patients with pathologically proven B cell non Hodgkin lymphoma whom will start chemotherapy

treatment with CHOP regimen, patients were excluded if already started their treatment protocol, having previous history of malignancy, presence of secondary malignancy, CNS lymphoma or aged less than 18years. All patients will be subjected to full medical history including duration of disease and comorbidities.

Clinical assessment emphasizing on presence or absence of pallor , purpuric eruption, fever, jaundice and lymph nodes examination including spleen and assess local examination for hepatomegaly, Despine sign and presence of any neurological affection either motor, sensory or cranial nerve affection and perform disease staging according to Ann Arbor staging system .Full investigations including (liver function tests (ALT,AST ,Albumin, ALP ,Total , direct bilirubin, PT, APTT and INR) , kidney function tests(creatinine ,urea and uric acid) ,complete blood counts and serum LDH done every cycle of chemotherapy. Bone marrow examination done before starting treatment and fulfilled all radiological investigations including (CT scan &PET scan done before, after 3 cycles and after completion of 6 cycle CHOP chemotherapy). CA125 levels measured at time of diagnosis and after completion of chemotherapy. Data management and statistical analysis were done using SPSS vs.25. Numerical data was summarized as means and standard deviations or medians and ranges. Categorical data was summarized as numbers and percentages. CA125 pre and post treatment were compared using Wilcoxon signed ranks test. CA125 pre-treatment was compared between different parameters using Mann Whitney U test or Kruskal Wallis test “for ECOG performance status”.

CA125 pre and post treatment were compared between different responses using Kruskal Wallis test. Correlation analysis was done using Spearman’s correlation. “r” is the correlation coefficient. It ranges from-1 to +1(-1 indicates strong negative correlation. +1 indicates strong positive correlation while 0 indicates no correlation). All P values were two sided. P values were adjuster for multiple comparisons. P values less than 0.05 were considered significant.

Results:

The study was conducted on 42 patients ,including 22 male patients (52.4%) and 20 females (47.6%,)including various age groups ranging from 19 to 65 years with mean age of 40 years and the standard deviation was 13, their mean body mass

index was 26.76 kg/m^2 and the standard deviation was 2.4.

***** Regarding Ann Arbor staging system ,the median stage in our study was 3 ranging from 2 to 4, however ,in consequence of presence or absence of constitutional manifestation, there was 27 patient with A symptoms (64.3%) and 15 patient with B symptoms (35.7%) but in ECOG performance status the median was 2 ranging from 1 to 3.

Regarding the pathological types of the studied group , the majority were of diffuse large B cell lymphoma in 35 patient (83.3%) followed by follicular lymphoma in 5 patient (11.9%) then nodal marginal zone lymphoma and small lymphocytic lymphoma 1 patient for each (2.4%). The mean lactate dehydrogenase level was 726 U/L with standard deviation 365 U/L. Clinical and radiological studies revealed that cervical and axillary lymphadenopathy were the most 2 frequent presenting features in 38 patients (90.5%) followed by inguinal lymphadenopathy and splenomegaly in 17 patients (40.5%) then abdominal lymphadenopathy in 15 patients (35.7%) then hepatic involvement in 6 patients (14.3%) followed by pulmonary ,mediastinal and pleural effusion in 5 patients(11.9%).but the least 2 frequent presenting features were ascites in 2 patients (4.8%) followed by gastric lymphoma in 1 patient (2.4%). On consequence of patients response after chemotherapy the majority of patients have partial remission in 18 patients (42.9%) followed by complete remission in 15 patients (35.7%) but the minority were to those with progressive disease in 9 patients (21.4%)**.**

*There was a positive correlation between CA125 levels before treatment and severity of the stage of the disease (r value 0.714, P< 0.001), lactate dehydrogenase levels (r value 0.811, P value <0.001), ECOG performance status (r value 0.444 and P value < 0.003), however there were no significant correlation between CA125 level before treatment and age or body mass index**.(Table 1)**

		CA125 before
Age	R	0.263
	P value	0.092
Body mass index	R	0.214
	P value	0.173
Stage	R	0.714**
	P value	<0.001
ECOG performance status	R	0.444**
	P value	0.003
Lactate dehydrogenase levels	R	0.811**
	P value	<0.001

*levels of CA 125 before treatment was higher in those with bone marrow involvement than those without (P value<0.001)

*In this study CA125 levels before treatment were significantly higher in those with pulmonary nodules than those without (P value was 0.003), Also it is higher in those with hepatomegaly than those without (P value less than 0.001), and it was higher in those with splenomegaly than those without (P value equal to 0.001).Corresponding to abdominal lymphadenopathy CA125 levels before treatment were significantly higher in those affected than those without (P value equal to 0.001) ,also CA125 levels before treatment were significantly higher in those with pleural effusion than those without(P value less than 0.001) .However, there was no significant difference in CA125 levels before treatment in those with and without cervical, axillary ,mediastinal and inguinal lymphadenopathy.

In this study, there was an overall significance in relation between CA125 levels before treatment and different categories of response criteria (P value less than 0.001), being higher in those with progressive disease than in those with partial remission (p value 0.045),also its level is higher in those with progressive disease than in those with complete remission (p value less than 0.001), also it levels were higher in those with partial remission than in those with complete remission (P value 0.001), so we stated that

the more the pretreatment CA125 elevation ,the worse the response to chemotherapy. In this study levels of CA125 after treatment in patients with complete remission were significantly lower than that before treatment (P value was 0.011).also in those with progressive disease CA125 levels before treatment are significantly lower than that after treatment (P value 0.038) but there is no statistical significance as regarding CA 125 levels before and after treatment in those with partial remission (**Table 2**).

CA125 before		**CA 125 after**	
Pair	**P value**	**Pair**	**P value**
CR vs. PR	0.001	CR vs. PR	<0.001
CR vs. PRO	<0.001	CR vs. PRO	<0.001
PR VS PRO	0.045	PR VS PRO	0.02

Discussion:

In this study, there was a positive correlation between CA125 levels before treatment and advanced stage (P value less than 0.001), A study done in 2004 get in concordant with our results with a positive correlation between CA125 and advanced stage (P value 0.07) [5] and another study done in 2002 was convenient with our result in affirming the positive correlation between pretreatment elevation in CA125 and advanced stage (p value 0.023) **[5 and 6]** In this study there was a positive correlation between pretreatment elevation in CA125 and bad ECOG performance status (P value less than 0.003). The results of the study performed 2004 were in concordant with our results with a positive correlation between pretreatment elevation in CA125 and bad ECOG performance status (P value 0.02) [5]

In this study there was a positive correlation between pretreatment elevation in CA 125 and LDH and (P value less than 0.001)), *The studies* **[5 and 6] were** aligned with our results with a positive correlation between CA125 and LDH (P value 0.01) ,and (p value 0.001) respectively **[5 and 6]**.

Regarding the relation between pretreatment elevation in levels of CA125 and (age, sex, body mass index) there was no significant relation detected. This was proved by others [7], CA125 level before treatment and age [8] and between pretreatment elevation in CA125 and sex **[**6]

In this study CA125 levels before treatment were significantly higher in those with pulmonary nodules than those without (P value was 0.003), Also it was higher in those with hepatomegaly than those without (P value less than 0.001), and it was higher in those with splenomegaly than those without

(P value equal to 0.001).Corresponding to abdominal lymphadenopathy CA125 levels before treatment were significantly higher in those affected than those without (P value equal to 0.001) also CA125 levels before treatment were significantly higher in those with pleural effusion than those without(P value less than 0.001) .However, there was no significant difference in CA125 levels before treatment in those with and without cervical, axillary ,mediastinal and inguinal lymphadenopathy. It was stated that high CA125 level in B cell NHL patients was associated with abdominal involvement, and extranodal extension [9], which was correspondent to our study but in contrary they emphasize high levels of CA125 in those with mediastinal affection that was non concordant with present study and that could be explained by in this study we have 83.3% of the studied patients having aggressive types of B cell non Hodgkin lymphoma and mediastinal involvement is not uncommon as a presenting feature in contrary. A study proposed that there was larger scale of patient with indolent lymphoma 60% with 40% to aggressive types leading to this significant relation [9]. The study done 2004, [5] was also corresponding to our results as they collectively associate any extranodal presenting feature in relation to pretreatment elevation in CA125 and stated that its level was higher in patients with extranodal affection than those without (P value 0.004). Some researchers affirmed the association between CA125 pretreatment elevation and extra-nodal involvement (p value less than 0.001) [8]. Also the relation between pretreatment elevation in CA125 levels and extranodal involvement that was restricted in this study to abdominal involvement (P values less than 0.05*)* and pleural effusion (less than 0.01) was assured [10],

Likewise in *2005 a* study on patients with significant pretreatment elevations of CA 125 levels showed that they were having abdominal and serosal involvement (p value less than 0.05).and it also confirms the non-significant relation between presence of mediastinal involvement and pretreatment elevation in CA125 [11]. The study done in 2002 was convenient with our results in affirming the relation between pretreatment elevation in CA125 and presence abdominal involvement (p value 0.002) and between it and presence of pleural effusion (p value equal to 0.006) , but this study was non convenient with our study in the point of non-significant relation between presence of mediastinal involvement and pretreatment

elevation in CA125 which was significant in the former study and the explanation was as mentioned before as this study patient were 56% indolent types and 44% were with aggressive pathology [**9, 5, 8, 10, 11 and 6]**

In this study, there was a significant pretreatment elevation in the levels of CA125 in those with bone marrow involvement than those without (P value less than 0.001) and that was consistent with others that confirm this result (p value equal to 0.05).

In this study, there was an overall significance in relation between CA125 level before treatment and different categories of response criteria (P value less than 0.001), being higher in those with progressive disease than in those with partial remission (p value 0.045),also its level was higher in those with progressive disease than in those with complete remission (p value less than 0.001), also it levels were higher in those with partial remission than in those with complete remission (P value 0.001), so we stated that the more the pretreatment CA125 elevation ,the worse the response to chemotherapy. That was consistent with others [10] that confirmed this result as pretreatment CA125 levels were lower in those with complete remission than those with progressive disease (p value equal to 0.05). The study done in 2004 [5] was convenient with this study in that there was significant pretreatment elevation in CA125 levels in those with partial response and progressive disease than those with complete remission (p value 0.06). The study done 2002 [6] was harmonious with us in that patients who achieved complete remission had lower CA125 levels compared to those with partial remission or progressive disease *(p value* 0.001)

In this study, there was an overall significance between CA 125 levels after treatment in relation to different categories of response criteria (P value less than 0.001), being higher in those with progressive disease than in those with partial remission (P value 0.02). Also it is higher in those with progressive disease than in in those with complete remission (P value less than 0.001), likewise it is higher in those with partial remission than in those with complete remission (P value less than 0.001). The results of that study done in *2004* [5] were convenient with this study results as they found that the lowest values of CA125 after treatment were in patients achieved complete remission. However, patients with partial remission and those with progressive disease having higher

levels of CA125 (p value 0.06). Also it was found that the after treatment CA125 levels were lower in those with complete remission than patients with partial remission and those with progressive disease (p value 0.06) [6]

In this study levels of CA125 after treatment in patients with complete remission were significantly lower than that before treatment (P value was 0.011).also in those with progressive disease CA125 levels before treatment are significantly lower than that after treatment (P value 0.038) but there is no statistical significance as regarding CA 125 levels before and after treatment in those with partial remission. It was found that levels of CA125 after treatment in those with complete remission were lower than that before treatment (p value 0.001), also they found that CA125 levels were higher after treatment than before treatment in those with progressive disease (p value 0.01) [5] which was convenient with this study. However, it was non convenient in the point of significant increment in level of CA125 after treatment than that before treatment in those with partial response (p value 0.007). It was found that among all presenting patients, all complete responders had normalization of the values by the end of the treatment [10]. This was concordant with our study. In contrast, the non-responding patients maintained CA125 levels above the normal limit throughout therapy (p value was 0.01) in their study they associate both categories of patients with partial remission and those with progressive disease as one group.

Conclusion:

Higher levels of CA-125 before treatment were associated with advanced, extranodal disease and poor response to chemotherapy..

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