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ROLE OF SERUM LDH LEVELS IN PROGNOSTICATION OF PATIENTS DIAGNOSED OF HODGKIN'S LYMPHOMA: A PROSPECTIVE COHORT STUDY

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ABSTRACT

Hodgkin's lymphoma (HL) constitutes around 30% of all lymphomas . IPS is used for the risk stratification of advanced stage HL but it lack applicability to the early stage cases ..In this prospective cohort study, we aim to confirm the relationship between hsCRP levels with treatment response (interim as well as end of treatment) of HL treated with the standard chemotherapy and radiotherapy regimens. A total of 50 patients were recruited over a period of 18 months and the patients were followed up in the hematology clinic and interim treatment responses as well as end of treatment response were assessed. Correlation of the serum LDH levels and the treatment response showed that the low levels of serum LDH level were associated with more advanced stages.. Univariate analysis showed that there was no significant correlation of interim treatment response as well as end of treatment response with serum LDH levels .

KEYWORDS :

INTRODUCTION

Classical HL represent nearly 95% of all the cases of HL(2).A cure can be achieved in approximately 80% of the patients with current treatment regimen consisting of multi agent chemotherapy and radiotherapy (in selected cases).The remaining 20% attaining remission(4).Early identification of the patients who would fail treatment or relapse in future is currently a challenge. At present the most commonly used tool for prognostication of HL cases is international prognostic score(IPS) (on a scale of 0 -7), with higher scores indicating poorer prognosis)(5).This score is a combination of clinical and basic haematological parameters recorded at the time of diagnosis of a case like age , gender ,stage, haemoglobin level ,albumin level and lymphocyte counts (1). Children and adolescents with classical Hodgkin's Lymphoma (HL) have an excellent prognosis . For these patients the prognostic role of stage IV, extranodal involvement, presence of B-symptoms, bulky disease, number of involved lymph nodes and elevated Erythrocyte sedimentation rate (ESR) was demonstrated by several studies. Lactate dehydrogenase (LDH), a cytoplasmic enzyme, reversibly catalyzes the conversion of pyruvate to lactate, which is the last step of glycolysis. Even under normal oxygen concentrations in malignancies, Pyruvate transformation to lactate is upregulated. The tumor microenvironment acidification can promote tumor progression and metastasis. There are many tissues in which LDH is widely expressed, such as heart, muscle, and various tumors, and it is detectable in serum. High serum lactate dehydrogenase (SLDH) levels have been reported as a poor prognostic indicator in non small cell lung cancer, malignant lymphoma, pancreatic carcinoma, and colorectal cancer7-10. Furthermore, current European and American Joint Committee on Cancer (AJCC) recommend SLDH as a staging and progression marker in melanoma11. In addition, high LDH protein expression also correlates with poor outcome and metastasis in many solid tumors. In this study we aim to study the role of serum LDH levels to prognosticate the patient of Hodgkin's lymphoma .

MATERIAL AND METHODS

Study Design

This was a prospective cohort study carried out in the patients diagnosed with Hodgkin's lymphoma who completed treatment at PGIMER, Chandigarh.

Patients were enrolled in the study from the Adult Haematology Clinic PGIMER, Chandigarh prospectively from July 2017 to March 2018 and then they were followed up till November 2018.

Duration Of The Study

July2017 – December. 2018

Place Of The Study:

1.Department of Internal Medicine Adult Clinical Haematology Unit PGIMER,Chandigarh
2. Department of Histopathology, PGIMER, Chandigarh

Inclusion Criteria

1.Primary diagnosis of Hodgkin's lymphoma confirmed by a tissue biopsy
2. Adequate lymph node tissue in the paraffin block
3. Treatment naive patients

Exclusion Criteria

1. Patient previously treated with chemo radiotherapy before coming to PGIMER,. Chandigarh.
2. Patients who did not complete chemotherapy or end of treatment chemotherapy response assessment were excluded from further analysis.

METHODOLOGY

Procedure

1. Demographic and disease data were recorded in a predesigned performa (annexure 3) and investigations were recorded as per the performa.

2. Collection of the clinical and the laboratory data of the newly enrolled cases was done in the study performa.

3. Biopsy numbers of the lymph node were taken from the Adult Haematology Clinic case record files and the paraffin block were retrieved from the archive of the Department of Histopathology.

4. Cases with adequate tissue in the paraffin block in the archives of the Department of Histopathology were selected and immunohistochemistry staining was performed.

5. Serum LDH levels were done before starting the treatment of the patients fulfilling the inclusion criteria.

6. Correlation of LDH levels , and treatment response (interim as well as end of treatment response was assessed.

7. The interim treatment response was assessed with the PET CT SCAN after two cycles of the chemotherapy and the response was assessed by the Deauville criteria.

8. The end of treatment response was assessed with the

PETSCAN after completion of chemotherapy and the response was assessed by Deauville criteria.

Statistical Analysis

The descriptive statistics were used to study the response rates, Correlation was assessed between LDH levels and the response rate by using Chi square test. .Differences were considered as significant if the computed p value was less than theoretical p value i.e. 0.05. Univariate analysis was performed to assess the association between the LDH levels with the treatment response with SPSS, version 22.0.

RESULTS

During the study period, we recruited 60 consecutive, treatment naive patients of Hodgkin's lymphoma. Out of this cohort, there were few exclusions as following:

A. Three patients died before starting treatment.

B. Seven patients lost to follow up before completion of therapy.

Hence, their response ~to chemotherapy was not available (due to leaving the treatment before completion). Therefore, in the end, total 50 patients were selected. The patients were followed up in the hematology clinic and interim treatment responses as well as end of treatment response were assessed.

Serum LDH LEVELS:

Lactate dehydrogenase levels were measured in the patients under our study with the cut off values of 400U/L; in which 59.6% of the patients were reported with LDH cut off values less than 400U/L with 40.4% of patients having values greater than 400U/L. Mean absolute value was 374U/L. Higher LDH levels (>400U/L) were present in the advanced stages as compared to early stages. However, there was no significant correlation (p value 0.590) found between mean absolute value of LDH in early and advanced stages of disease.

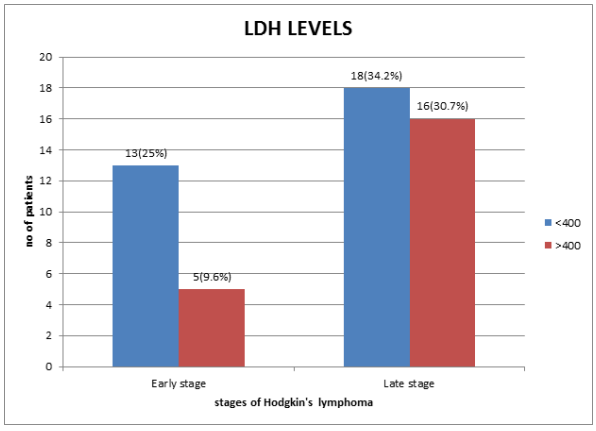

Figure.1.LDH levels in various stages of disease.

ANALYSIS:

Interim Treatment Response:

Univariate analysis showed that total of 48 patients 19(39.5%) had serum LDH levels <400 and 29(60.4%) had serum LDH levels >400 ,similarly a total of 4 patients not in complete remission 2(50%) had serum LDH levels <400 and 2(50%) had serum LDH levels >400 Also, there was no significant correlation of interim treatment response with serum LDH levels as shown in table no 1.

End Of Treatment Response:

Univariate analysis showed that total of 48 patients in complete remission 39(60.4%) had serum levels <400 and 19(39.5%) had serum LDH levels >400, similarly a total of 4 patients not in complete remission 2(50%) had serum LDH levels <400 and 2 patients (50%) had serum LDH levels >400.Also,there was no significant correlation of end of treatment response with serum LDH levels as shown in table no 2.

Characteristics Of Patients With Interim Treatment Response

Features	Number of patients in complete remission N(%)	Number of patients not in complete remission N(%)	P value
Serum LDH levels			
<400	19(39.5%)	2(50%)	0.683
>400	29(60.4%)	2(50%)	

Characteristics Of Patients With End Of Treatment Response

Features	Number of patients in complete remission N(%)	Number of patients not in complete remission N(%)	P value
Serum LDH levels			
<400	29(60.4%)	2(50%)	0.377
>400	19(39.5%)	2(50%)	

DISCUSSION

In this study, which is the prospective investigation carried out over a period of 18 months based on data available,we observed no association between circulating hsCRP concentration and overall risk of Hodgkin's lymphoma. Among biochemical parameters, lactate dehydrogenase (LDH) represents a very valuable enzyme in patients with malignant lymphomas. The serum level has been considered as very important in the evaluation of disease extension in non- Hodgkin's lymphomas (NHL) and Hodgkin's disease (HD).This finding agrees with that, reported by other investigators .This intense LDH level observed in patients during cancerous conditions may be the result of high glycolytic rate. In fact, the high glycolytic rate is important for rapidly proliferating cancers . Protein kinases, various hormones and growth factors have been shown to regulate LDH gene expression . In most cases, these factors induce a shift towards A-subunit containing isoenzymes which can derive more energy under anaerobic conditions. Furthermore, it has been shown that TNF is capable of inducing LDH-A expression in cultured Sertoli cells. Human lymphoma cells obtained from fresh tumor samples have been shown to produce TNF. It is therefore possible that the serum LDH alterations observed in lymphoma patients may be due to the production of inflammatory cytokines. The importance of serum LDH as a direct indicator of tumor burden has already been pointed out in other clinical studies . Indeed, mechanisms for energy production involved in cell duplication require a high LDH cell content and renewal of NAD resynthesis, in support of a continuing glycolysis. For a given tumor bulk LDH production is conceived as being proportional to its metabolic and proliferative activity. Accordingly, high LDH production suggests either large tumor bulk or a fast proliferation in a smaller tumor, and this could explain an aggressive course and a poorer response to therapy . In addition, the tumor cells may produce LDH enzyme to respond to the increase of lactic acid, resulting in oxidative reductive reaction to become pyruvic acid. High LDH level describes high aggressiveness and proliferation of the tumor cells. Therefore, LDH level in NHL is a marker of cell turnover and correlated with tumor burden. Several studies showed correlation between LDH level and the result of therapy. High LDH level often provides less response to the result of therapy, often relapses, and has a potential of metastasis. Lactate efflux provokes a local inflammatory response that attracts immune cells such as macrophages, which secrete cytokines

and growth factors that drive tumor cell growth and metastasis. Indeed, the inflammatory response is often necessary for tumor progression, and elevated numbers of inflammatory cells, such as tumor-associated macrophages, connote poor prognosis. Furthermore, lactate in the tumor cell milieu impairs the adaptive immune response, disabling immune surveillance. Thus, lactate also appears to promote tumorigenesis via non–tumor cell mediated effects on the inflammatory and immune responses. In the present study, we intended to correlate hsCRP levels with treatment response and survival outcomes but due to short follow up period of our study with only 4 relapses and no mortality, the effective number of events were very less. Hence we limited our study end point to treatment response only. Although present study put forward some evidence which bridge the gap of existing knowledge about role of M1 and M2 tumor related macrophages phenotype in treatment response in patients with HL, there still exist some limitation in present study.

CONCLUSION

In conclusion, higher levels of serum LDH were associated with advanced stages.There was no significant correlation between serum LDH levels with the treatment response interim as well as end of treatment response.

REFERENCES

1. Increased Level of Lactate Dehydrogenase Correlates with Disease Growth in Algerian Children with Lymphoma Galleze A1,2, Raache R1,2*, Cherif N3 , Eddaïkra A2 , Belhani M3 , Bensenouci A3 , Touil-Boukoffa C1 , Abbadi M C2 , Attal N
2. Serum lactate dehydrogenase level as a prognostic factor in Hodgkin's disease Servicio de Hematologia/Departamento Medicina Hospital Universitario, Universidad de Salamanca, Salamanca, Spain R. Garcia, J.M. Hernandez, M.D. Caballero, M. Gonzalez, J. Galende, M.C. del Cainizo, L. Vazquez & J.F. San Miguel
3. Prognostic Factors in Hodgkin's Disease: Multivariate Analysis of 327 Patients from a Single Institution Piotr Smolewski,1 Tadeusz Robak, Euzebiusz Krykowski, Maria Blasin˙ska-Morawiec, Hanna Niewiadomska, Anna Pluzanska, Ewa Chmielowska, and Oscar Zambrano Departments of Haematology [P. S., T. R., E. K., M. B-M.], Pathology [A. P, E. C., O. Z.], and Chemotherapy [H. N.], Medical University of Lodz, 93-513 Lodz
4. Serum Lactate Dehydrogenase (LDH) as a Prognostic Index for Non-Hodgkin's Lymphoma" LUIGI ENDRIZZI, MARIO V. FIORENTINO,t LUIGI SALVAGNO, ROMANA SEGATI, GIOVANNI L. PAPPAGALLO and VINICIO FOSSER Divisione di Oncologia Medica, Ospedale Civile, 35100 Padova, Italy.