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Free Light Chain Abnormalities in Diffuse Large B Cell Lymphoma

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Original Research Article

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Abstract: In diffuse large B-cell lymphomas (DLBCL), increased serum FLC correlated with advanced disease stage and poorer outcome . We studied the free light chain abnormalities in patients with newly diagnosed diffuse large B cell lymphoma planned for curative treatment. Blood samples send for FLC analysis before staring treatment and we correlated serum free light chain abnormalities (FLC) with various disease prognostic factors of DLBCL.
Keywords: B-cell lymphomas (DLBCL), bnormalities

AIM

To study the free light chain abnormalities in patients with newly diagnosed diffuse large B cell lymphoma.

INTRODUCTION

The serum free light chain (FLC) assay quantitates free kappa and free lambda immunoglobulin light chains. This assay has prognostic value in MGUS, multiple myeloma (MM), solitary plasmacytoma, and amyloid light chain (AL) amyloidosis, and has been incorporated in response criteria for both MM and AL amyloidosis [1]. Incidence of abnormal FLC varied from 0% to 36% in Non-Hodgkin's Lymphoma (NHL) [2, 3]. In diffuse large B-cell lymphomas(DLBCL) , increased serum FLC correlated with advanced disease stage and poorer outcome and was demonstrated as an independent, adverse prognostic factor for overall/event-free survival[4].

MATERIALS & METHODS

This Study was conducted in patients who were newly diagnosed with DLBCL in the Department of Medical oncology in a Tertiary Cancer care Centre. After taking an informed consent, a detailed clinical examination was carried out. Standard Staging work up for DLBCL including complete blood counts, Serum biochemistry with Liver function tests, Renal function tests, Serum Electrolytes, CT Neck, Chest, Abdomen and Pelvis, Bone marrow examination was also send.

Blood samples will be sending for FLC analysis in biochemistry lab of RCC. All staging work up and treatment will be as per the Department policy and the data will be collected. Then patient will be followed up for treatment response and survival.

Inclusion criteria includes newly diagnosed patient with DLBCL, Patients planned for curative treatment. Exclusion criteria includes newly diagnosed DLBCL who received prior treatment other than steroids, relapsed DLBCL and those patients with elevated serum creatinine (>1.4mg/dl).

RESULTS

The total number of study population was 60 patients. The baseline characteristics of DLBCL study population is given in the Table 1. The Age of the patients range from 25 years to 90 years. The median age at diagnosis was 54 years .About 53% patients are males and 47% are females. Mean duration of symptoms was 3 months. B symptoms were present in 19 patients (32%).

Lymphadenopathy was seen in 44 patients (73%). Organomegaly seen in 19 patients which included hepatomegaly in 16% and splenomegaly in 15%.

Twenty three patients (38%) presented with abdominal lymphadenopathy in the form of paraortic mass, mesenteric mass, retroperitoneal mass, lumbar

mass. Gastro intestinal involvement was seen in 10 patients (26%). Ileum involved in 4%of cases, followed by stomach, jejenum, appendix, caecum and duodenum. Ten patients (10%) presented with mediastinal mass,2 patients with pleural effusion.

Anemia was seen in 7 patients(12%).ESR elevated in 7 patients(12%).On differential count examination, Neutrophilic leucocytosis seen in 46 patients(68%), eosinophilia reported in 9(15%), Lymphocytopenia in 19(32%),Lymphocytosis 2(3%), monocytosis in14(23%). LDH was elevated in 88% patients. No patients presented with Tumour lysis syndrome.Liver function abnormality seen in 8% with elevated serum bilirubin.Alkaline phosphatase elevated in 23%. Hypercalcemia noted in 10%.Hyperphosphatemia in 20%. Nine patients (15 %%) had Ann Arbor stage IV disease. Twenty patients(33%)had Ann Arbor stage III disease .Eighteen patients (30%) had Ann Arbor stage II and 13 patients (22%)had stage I disease . Bone marrow infiltration was seen in 3 patients (5%). Ten patient (26%) had Bulky disease. High MIB >25% was seen in 67%. Immunohistochemistry showed immunoreactivity of LCA (100%), CD20+ (100%), BCL 6+(57%), CD10+(3%),CD 10 negative 12%. Five patients (5%) had CNS symptoms at presentation and 2 patients (3%) had CSF positive disease. Extra nodal involvement was seen 23 patients (38%).

Most common extra nodal involvement was with gastrointestinal sites followed by testes, liver, thyroid, oropharynx, orbit, nasopharynx, bone, scalp and extradural lumbosacral mass. Among gastro-intestinal sites, commonest involved site was Ileum followed by stomach, jejenum, caecum, appendix and duodenum.

The IPI (International prognosis index) was calculated as low risk (L-IPI 0-1) in 20 patients (33%), low- intermediate risk (LI-IPI 2) in 9 patients (15%), high-intermediate risk (HI-IPI 3) in 26 patients (43%) and High risk (H-IPI 4-5) in 5patients (9%). Table 2 shows the free light chain abnormalities in DLBCL study population. In this study cohort, serum free Kappa was range from 16.2 - 129.2 and serum free Lamda range from 14.6-52.1 .About 55 patients (91%) had elevated sFLC- Kappa and 31patients (51%) had elevated sFLC- Lamda. Kappa/lamda ratio range from 0.59-4.7. Median Kappa/lamda ratio was1.1. Among these patients, 8 patients (13%) harbored abnormal Kappa/ Lamda ratio. Table 3 shows Kappa/Lamda Ratio in relation to stage ,extra nodal and IPI risk category .Ann Arbor stage III or IV disease had more number of patients with elevated sFLC-abnormal Kappa/ Lamda ratio.Stage I or II disease with extra nodal involvement had elevated sFLC with abnormal Kappa/ Lamda ratio. Out of 23 patients with extra nodal involvement, 5 patients (22%) had elevated sFLC with abnormal Kappa/ Lamda ratio. Sub set analysis of Eight Abnormal K/L Ratio patients in relation to stage and extra nodal involvement shown in Table 4. Abnormal Kappa/ Lamda ratio was seen frequently with high-intermediate risk (HI-IPI) , low- intermediate risk (LI-IPI) and low risk (L-IPI) with more of extra nodal presentations. Patients with elevated sFLC and abormal K/lamda ratio did not differ significantly with respect to gender, serum LDH levels and B symptoms.

Table-1: Baseline Characteristics of DLBCL study population

Age	25-90 Years	
median Age	54 years	
Median duration	3 months	
male	32	53%
female	28	47%
Lymphadenopathy	44	73%
Hepatomegaly	10	16%
Splenomegaly	9	15%
B symptoms	19	32%
Abdominal Lymphadenopathy	23	38%
GIT involvement	10	26%
Neurological involvement	5	10%
HB< 10 mg/dL	7	12%
ESR >100	7	12%
Neutrophilic leucocytosis	41	68%
Eosinophilia	9	15%
Monocytosis	14	23%
Lymphocytopenia	19	32%
Lymphocytosis	2	3%
LDH <500	7	12%
LDH >500	53	88%
SBR >1.4	5	8%

SALP>147 IU/L	14	23%
Phosphrous >4.5 mg/dL	12	20%
Calcium >10.2 mg/dL	5	10%
Mediastinal mass	5	10%
Pleural effusion	2	3%
CSF Infiltration	2	3%
Extra nodal involvement	23	38%
BM Infiltration	3	5%
STAGE 4	9	15%
3	20	33%
2	18	30%
1	13	22%
MIB >25%	40	67%
MIB<25%	20	33%
Low risk IPI 0-1	20	33%
Low Intermediate risk IPI 2	9	15%
High intermediate riskIPI3	26	43%
High risk IPI4-5	5	9%
Immunophenotyping		
LCA+	60	100%
CD20+	60	100%
BCL 6+	34	57%
CD10+	2	3%
CD10-	7	12%

Table-2: Free light chain abnormalities in DLBCL Study population

KAPPA	16.29(min) - 129.2(max)
KAPPA Elevation	55/60 patients (91%)
LAMDA	14.6(min)- 52.1(max)
LAMDA Elevation	31/60 patients (51%)
Kappa/Lamda RATIO	0.59(min)- 4.7(max)
Median kappa/lamda Ratio	1.1

Table-3: Kappa/Lamda Ratio in relation to stage, extra nodal and IPI risk category

variables	Abnormal K/L Ratio	Normal K/L ratio
	Stage of DLBCL	
stage 1	2	10
Stage 2	1	18
stage 3	1	17
stage4	1	6
Extra nodal	5	18
Low risk IPI 0-1	3	17
Low Intermediate risk IPI 2	1	8
High risk IPI4-5	4	5

Table-4: Sub set analysis of Eight Abnormal K/L Ratio patients in relation to stage and extra nodal involvement

STAGE	K/L Ratio
1AE	1.66
3B	1.76
1AE	1.8
2AE	2.2
3AE	2.5
4A	2.9
3AE	3.54
3A	4.7

DISCUSSION

Diffuse large B-cell lymphoma (DLBCL) is the most common non-Hodgkin's lymphoma (NHL). Several studies also showed that sFLC abnormalities were associated with poor outcome in patients with chronic lymphocytic leukemia, mantle cell lymphoma, Hodgkin lymphoma. However, the data on sFLC are limited in DLBCL. Serum FLC abnormalities are prevalent in patients with DLBCL, with 32% having elevated or concentrations and 14% of patients having an abnormal: FLC ratio. There are several causes of elevated FLC in patients with DLBCL such as renal dysfunction,advanced age, or immune disruption or stimulation however our study excluded patients with elevated renal function. In the present study, 91% patients had an elevated sFLC or concentrations. This frequency was much higher than that found in previous studies [4].

In this study cohort, about 55 patients (91%) had elevated sFLC- Kappa and 31patients (51%) had elevated sFLC- Lamda. Only 8 patients (13%) harbored abnormal Kappa/ Lamda ratio. Jardin *et al.* recently also reported that elevated sFLC was strongly associated with PFS and OS in DLBCL patients on uni-variate analysis, but after adjusted for IPI, it is only significantly associated with OS[5].

Increased serum FLC was strongly associated with an inferior outcome and remained significant after adjusting for IPI. Abnormal: FLC ratio, however, was only modestly associated with outcome across all patients, with the association only related to a concomitant elevated FLC [4]. However our study shows that abnormal Kappa/ Lamda ratio was seen frequently with high-intermediate risk (HI-IPI), low-intermediate risk (LI-IPI) and low risk (L-IPI) with more of extra nodal presentations.

Advanced disease and early Stage I or II disease with extra nodal involvement had elevated sFLC with abnormal Kappa/ Lamda ratio in our study further reveals that there is an association of elevated FLC with stage and extranodal sites involvement and it could be a reliable marker for disease burden.

CONCLUSION

Ninety one percent patients had elevated serum FLC- Kappa and 51% had elevated serum FLC- Lamda at disease presentation. Abnormal Kappa/ Lamda ratio was detected in 13% of DLBCL cohorts. Advanced Ann Arbor stage III or IV disease, presence of extra nodal involvement, high-intermediate risk (HI-IPI), low- intermediate risk with extra nodal presentations had elevated sFLC with abnormal Kappa/ Lamda ratio. Patients with elevated sFLC and abormal K/lamda ratio did not correlate significantly with respect to gender, high serum LDH levels and presence of B symptoms.

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