Introduction

Lymphoma is classified into Hodgkin or non-Hodgkin type. NHL includes a heterogeneous group of lymphoid malignancies and sub classified according to an aggressive or an indolent clinical course and whether they have originated from Tor B-lymphocytes. ***(WHO Classification of Tumors of Hematopoietic and Lymphoid Tissues, ٢٠٠٨).***

Diffuse large B-cell lymphoma (DLBCL) is the most common type of the aggressive NHLs in the United States. Non-Hodgkin's lymphoma rates, including DLBCL, have continuously increased ٣٪ to ٤٪ each year in the U.S.A. from ١٩٧٣ to ١٩٩٠'s ***(Fisher, ٢٠٠٤).***

Endogenous immune response to cancer may be counterbalanced by number of immune 'checkpoints' used by tumors to avoid immune destruction ***(Chambers et al., ٢٠٠١).***

Studies in animals have shown that inhibition of these checkpoints reactivation immunity against cancer cells leading to new therapeutic drugs recently discovery in advanced cancer ***(Wolchok et al., ٢٠١٣)***.

Programmed death ١ (PD-١) protein is a key immune-checkpoint receptor expressed by activated T cells and it mediates immunosuppression. In tumor tissues, activated T cells can encounter the immunosuppressive PD-١ ligands PD-L١ (B٧-H١) and PD-L٢ (B٧-DC), both expressed by tumor cells and microenvironment as described in lymph proliferative diseases ***(Atanackovic et al., ٢٠١٤).***

It has been recently shown that the blockade of PD-١ or PD-L١ by monoclonal antibodies may lead to significant antitumor effects ***(Brahmer et al., ٢٠١٢).***

In DLBCL, PD-L١ has been reported expressed by tumor cells and PD-١ by tumor-associated T cells ***(Xerri et al., ٢٠٠٨).***

AIM OF THE WORK

This study will measure level of sPD-L١ in patients with DLBCL at baseline with correlation with patients' outcome.

Chapter (١)
Introduction of lymphoma

Lymphoma is a group of blood cell tumors that develop from lymphocytes (a type of white blood cell). The name often refers to just the cancerous ones rather than all such tumors.***(Taylor, Elizabeth, ٢٠٠٠)***

Epidemiology:

NHL is the ٨th most commonly diagnosed cancer in men and the ١١th in women. The disease accounts for ~٥.١٪ of all cancer cases and ٢.٧٪ of all cancer deaths. Areas with highest incidence of NHL include North America, Europe, Oceania, as well as several African countries**.**

(Mulleret al;٢٠١٠)

Signs and symptoms

Includeenlarged lymph nodes, fever, drenching sweats, unintended weight loss, itching, and constantly feeling tired. The enlarged lymph nodes are usually painless. The sweats are most common at night ***(National Cancer Institute, ٢٠١٤)***

Risk factors

For common types of non-Hodgkin lymphomas include autoimmune diseases, HIV/AIDS, infection with human

T-lymphotropic virus, immunosuppressant medications, and some pesticides***(National Cancer Institute, ٢٠١٤)***

Eating large amounts of red meat and tobacco smoking may also increase the risk***(Yang et al., ٢٠١٥)***

Diagnosis

If enlarged lymph nodes are present, is usually by lymph node biopsy. Bloodand bone marrow testing may also be useful in the diagnosis. Medical imaging may then be done to determine if and where the cancer has spread. Lymphoma most often spreads to the lungs, liver, and/or brain.***(National Cancer Institute, ٢٠١٤)***

Lymphoma is definitively diagnosed by a lymph node biopsy, meaning a partial or total excision of a lymph node examined under the microscope. This examination reveals histopathological features that may indicate lymphoma. After lymphoma is diagnosed, a variety of tests may be carried out to look for specific features characteristic of different types of lymphoma. These include:

- Immunophenotyping
- Flow cytometry
- Fluorescence in situ hybridization testing

(Mallick, Indranil; ٢٠١٢)

Staging and performance status

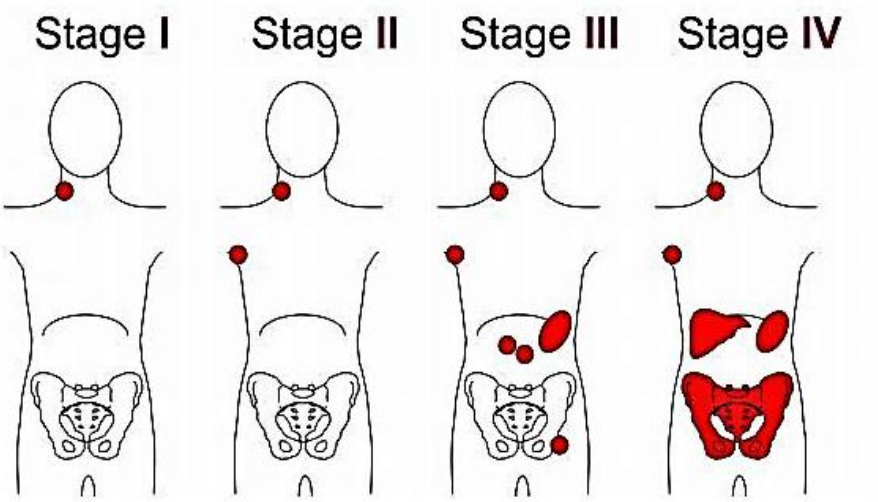
The staging is established according to the Ann Arbor classification system:

The Ann Arbor staging system is used to develop rational treatment strategies and is recommended for all non-Hodgkin's lymphomas, this system is based on the number and location of nodal and extranodal regions and takes symptoms into account.

Table ( ): Ann Arbor staging classification

Stage	
I	Involvement of a single lymphatic region (I) or localized involvement of single extra lymphatic organ or site (IE)
II	Involvement of two or more lymphatic regions on the same side of the diaphragm (II) or localized involvement of a single extra lymphatic organ or site and of one or more lymphatic regions on the same side of the diaphragm (IIE)
III	Involvement of lymphatic regions on both sides of the diaphragm
IV	Diffuse or disseminated involvement of one or more extra lymphatic organs with or without lymphatic involvement

(Cheson, et al ; ٢٠١٤)



Ann arbor staging

A:absence of B symptom.

B: fever, night sweats, weight loss.

X:bulky disease (widening of mediastinum by more than ٣٣٪ or mass more than ١٠ cm).

S :splenic disease.

E : involvement of a single extranodal site contiguous or proximal to known nodal site.

(Cheson et al., ٢٠١٤)

ECOG Performance Status

Table ( ): Developed by the Eastern Cooperative Oncology Group

Grade	ECOG performance status
٠	Fully active, able to carry on all pre-disease performance without restriction
١	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature, e.g., light house work, office work
٢	Ambulatory and capable of all self care but unable to carry out any work activities; up and about more than ٥٠٪ of waking hours
٣	Capable of only limited self care; confined to bed or chair more than ٥٠٪ of waking hours
٤	Completely disabled; cannot carry on any selfcare; totally confined to bed or chair
٥	Dead

(Okenet al; ٢٠١١)

Treatment

Prognosis and treatments are different for HL and between all the different forms of NHL, and also depend on the grade of tumour, referring to how quickly a cancer replicates. Paradoxically, high-grade lymphomas are more

readily treated and have better prognosis Burkitt lymphoma, for example, is a high-grade tumour known to double within days, and is highly responsive to treatment. Lymphomas may be curable if detected in early stages with modern treatment ***(Sweetenham; ٢٠٠٩)***

Low-grade lymphomas

Many low-grade lymphomas remain indolent for many years. Treatment of the non symptomatic patient is often avoided. In these forms of lymphoma, such as follicular lymphoma, watchful waiting is often the initial course of action. This is carried out because the harms and risks of treatment outweigh the benefits.***(Elphee; ٢٠٠٨)***

If a low-grade lymphoma is becoming symptomatic, radiotherapy or chemotherapy are the treatments of choice; although they do not cure the lymphoma, they can alleviate the symptoms, particularly painful lymphadenopathy. Patients with these types of lymphoma can live near-normal lifespans, but the disease is incurable. Some centers advocate the use of single agent rituximab in the treatment of follicular lymphoma rather than the wait and watch approach. Watchful waiting is not a good strategy for all patients, as it

leads to significant distress and anxiety in some patients. It has been equated with watch and worry. ***(Ansell ; ٢٠١٤)***

High-grade lymphomas

Treatment of some other, more aggressive, forms of lymphomacan result in a cure in the majority of cases, but the prognosis for patients with a poor response to therapy is worse.***(Bernstein., ٢٠٠٩)***

Treatment for these types of lymphoma typically consists of aggressive chemotherapy, including the CHOP or R-CHOP regimen. A number of people are cured with first-line chemotherapy. Most relapses occur within the first two years, and the relapse risk drops significantly thereafter ***(Jenkins , ٢٠٠٧)***

For people who relapse, high-dose chemotherapy followed by autologous stem cell transplantation is a proven approach.***(Philip; ١٩٩٥)***

Table ( ):٢٠١٦ WHO classification of mature lymphoid, histiocytic, and dendritic neoplasms

Mature B-cell neoplasms
Chronic lymphocytic leukemia/small lymphocytic lymphoma
Monoclonal B-cell lymphocytosis*
B-cell prolymphocytic leukemia
Splenic marginal zone lymphoma
Hairy cell leukemia
Splenic B-cell lymphoma/leukemia, unclassifiable
Splenic diffuse red pulp small B-cell lymphoma
Hairy cell leukemia-variant
Lymphoplasmacytic lymphoma
Waldenström macroglobulinemia
Monoclonal gammopathy of undetermined significance (MGUS), IgM*
μ heavy-chain disease
γ heavy-chain disease
α heavy-chain disease
Monoclonal gammopathy of undetermined significance (MGUS), IgG/A*
Plasma cell myeloma
Solitary plasmacytoma of bone
Extraosseous plasmacytoma
Monoclonal immunoglobulin deposition diseases*
Extranodal marginal zone lymphoma of mucosa-associated lymphoid tissue (MALT lymphoma)
Nodal marginal zone lymphoma
Pediatric nodal marginal zone lymphoma
Follicular lymphoma
In situ follicular neoplasia*
Duodenal-type follicular lymphoma*
Pediatric-type follicular lymphoma*
*Large B-cell lymphoma with IRF4 rearrangement**
Primary cutaneous follicle center lymphoma
Mantle cell lymphoma
In situ mantle cell neoplasia*

Diffuse large B-cell lymphoma (DLBCL), NOS
Germinal center B-cell type*
Activated B-cell type*
T-cell/histiocyte-rich large B-cell lymphoma
Primary DLBCL of the central nervous system (CNS)
Primary cutaneous DLBCL, leg type
EBV$^+$ DLBCL, NOS*
*EBV$^+$ mucocutaneous ulcer**
DLBCL associated with chronic inflammation
Lymphomatoid granulomatosis
Primary mediastinal (thymic) large B-cell lymphoma
Intravascular large B-cell lymphoma
ALK$^+$ large B-cell lymphoma
Plasmablastic lymphoma
Primary effusion lymphoma
*HHV8$^+$ DLBCL, NOS**
Burkitt lymphoma
*Burkitt-like lymphoma with 11q aberration**
High-grade B-cell lymphoma, with *MYC* and *BCL2* and/or *BCL6* rearrangements*
High-grade B-cell lymphoma, NOS*
B-cell lymphoma, unclassifiable, with features intermediate between DLBCL and classical Hodgkin lymphoma
Mature T and NK neoplasms
T-cell prolymphocytic leukemia
T-cell large granular lymphocytic leukemia
Chronic lymphoproliferative disorder of NK cells
Aggressive NK-cell leukemia
Systemic EBV$^+$ T-cell lymphoma of childhood*
Hydroa vacciniforme–like lymphoproliferative disorder*
Adult T-cell leukemia/lymphoma
Extranodal NK-/T-cell lymphoma, nasal type
Enteropathy-associated T-cell lymphoma

Monomorphic epitheliotropic intestinal T-cell lymphoma*
*Indolent T-cell lymphoproliferative disorder of the GI tract**
Hepatosplenic T-cell lymphoma
Subcutaneous panniculitis-like T-cell lymphoma
Mycosis fungoides
Sézary syndrome
Primary cutaneous $CD30^+$ T-cell lymphoproliferative disorders
Lymphomatoid papulosis
Primary cutaneous anaplastic large cell lymphoma
Primary cutaneous γδ T-cell lymphoma
Primary cutaneous $CD8^+$ aggressive epidermotropic cytotoxic T-cell lymphoma
*Primary cutaneous acral $CD8^+$ T-cell lymphoma**
*Primary cutaneous $CD4^+$ small/medium T-cell lymphoproliferative disorder**
Peripheral T-cell lymphoma, NOS
Angioimmunoblastic T-cell lymphoma
*Follicular T-cell lymphoma**
*Nodal peripheral T-cell lymphoma with TFH phenotype**
Anaplastic large-cell lymphoma, ALK^+
Anaplastic large-cell lymphoma, ALK^-*
*Breast implant–associated anaplastic large-cell lymphoma**
Hodgkin lymphoma
Nodular lymphocyte predominant Hodgkin lymphoma
Classical Hodgkin lymphoma
Nodular sclerosis classical Hodgkin lymphoma
Lymphocyte-rich classical Hodgkin lymphoma
Mixed cellularity classical Hodgkin lymphoma
Lymphocyte-depleted classical Hodgkin lymphoma
Posttransplant lymphoproliferative disorders (PTLD)
Plasmacytic hyperplasia PTLD
Infectious mononucleosis PTLD
Florid follicular hyperplasia PTLD*
Polymorphic PTLD
Monomorphic PTLD (B- and T-/NK-cell types)
Classical Hodgkin lymphoma PTLD

(Swerdlow, et al., ٢٠١٦)

Chapter (٢)
Diffuse large B cell lymphoma (DLBCL)

Definition:

Diffuse large B cell lymphoma (DLBCL) is the most common histological subtype of non-Hodgkin's lymphoma (NHL) accounting for ٣٠٪ of NHL. DLBCL is an aggressive lymphoma that affects patients of all ages, with a wide range of clinical presentations. The median age at presentation is ٦٤ years, with a slight male preponderance, and up to ٥٠٪ of patients present with advanced stages disease.***(Siegel et al., ٢٠١٣)***

Presentation:

Patients with DLBCL typically present with a rapidly enlarging lymph nodal mass, commonly in the neck or abdomen. ٣٠٪ of patients present with fever, night sweats and weight loss (B symptoms). Extranodal extramedullary disease occurs in up to ٤٠٪ of patients with DLBCL.***(Møller et al., ٢٠٠٤)***

The gastrointestinal tract is the most common site of extra nodal involvement; however, DLBCL can involve virtually any organ, including the central nervous system (CNS), salivary glands, nasal cavity and paranasal sinuses,

thyroid, breast, lung, liver, adrenal glands, kidneys and genital organs. Black race, male sex, age at diagnosis > ٦٠ years, advanced stage, and B symptoms at diagnosis are adverse prognostic factors **.*(Shenoy et al., ٢٠١١)***.

Risk factors:

The etiology of diffuse large B-cell lymphoma is unknown. Factors thought to potentially confer increased risk include immune suppression (including AIDS, and iatrogenic etiologies in the setting of transplantation or autoimmune diseases), ultraviolet radiation, pesticides, hair dyes, and diet

(Blinder, Fisher; ٢٠٠٨)

Pathophysiology:

DLBCL arises from mature B-cells at different stages of differentiation. Several gene mutations promote changes in B-cells, changing the gene expression and promoting a neo plastic transformation , during B lymphocyte ontogeny, after leaving the bone marrow, those cells travel to secondary lymphoid tissues where they will find their respective antigens promoting the development of secondary follicles. An antigen-dependent phase of B-cell development occurs at this site. In the germinal center of the secondary follicle,