Prognostic Value of Early Introduction of Second Line Chemotherapy in Patients with Diffuse Large B cell Lymphoma (Prospective Study)

Thesis

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ABSTRACT

Introduction: DLBCL is the commonest type of lymphoma. The mainstay of treatment is chemotherapy. Earlier response is associated with better survival. Anthracyclines are effective but cardiotoxic .

Methods : This is a randomized pilot trial of 50 adult patients with DLBCL conducted at Kasr Al Ainy oncology department ,ages 18 years-65 years) pathologically proven as DLBCL stages I bulky-IV according to Ann Arbor classification , ECOG Performance status < 3.Patients were treated with standard dose 3-weekly R-CHOP for 3 cycles. Those achieved partial remission were randomized to either continue R- CHOP or to shift to ESHAP +/- rituximab. All patients were randomized also to either receive prophylactic carvidolol plus enalapril or not to receive them. Troponin I, echocardiography Chest, abdomen and pelvic CT scan were used to re – assess the patients.

Results: 50 patients were enrolled between May 2013 and September 2014. median age was 51 years. Better outcome with non shift group (RR =90.9 % Vs 66.67%) .The 12 month DFS in the continue group was 75 % while in ESHAP group was 58% which is statistically significant (p value = 0.049). The 12 month OS was 100 % in the continue group versus 68 % in the ESHAP group which is statistically significant (p value =0.003). No early cardiotoxicity was encountered in the whole group.**Conclusion:** These results should be confirmed on larger scale studies.

Key words: (DLBCL-Early shift – anthracyclines induced cardiotoxicity)

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List of Abbreviations

ACE	:	Angiotensin converting enzyme.
ALCL	:	Anaplastic Large Cell Lymphoma.
ALK	:	Anaplastic lymphoma kinase.
ASCT	:	Autologous stem cell transplantation.
BCL 2	:	B cell lymphoma 2.
BCL 6	:	B cell lymphoma 6.
CSF	:	Cerebrospinal fluid.
DFS	:	Disease free survival.
DLBCL	:	Diffuse Large B cell Lymphoma.
EFS	:	Event free survival.
ECOG	:	The Eastern Cooperative Oncology.
GELA	:	Group d'etude des lymphoma de l' adult.
HDT	:	High dose therapy.
Ig	:	Immunoglobulin.
IGVH	:	Immunoglobulin Heavy Chain Variable Region.
IPI	:	International Prognostic index.
ITAM	:	Immunoreceptor Tyrosine Based Activation Motif.
Kb	:	Kilo-byte.
Mo	:	Months.
MYC	:	Myelocytomatosis .
NCCN	:	National Comprehensive Cancer Network.
OS	:	Overall survival.
PCR	:	Polymerase Chain reaction.
Vs	:	versus.

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INTRODUCTION

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL), and accounts for 30%–40% of all adult NHLs. **(Vaidya and Witzig, 2014).** NHL was ranked as the fifth most frequent cancer in Egypt **(Ibrahim et al., 2014).**

Although potentially curable, 40% of patients with DLBCL will die of relapsed or refractory disease. The standard of care for initial treatment of DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone on a 21-day schedule (R-CHOP21) for six cycles**. (Vaidya and Witzig, 2014)**

In latest version of NCCN guidelines (2015) for diffuse large B cell lymphoma, patients having stage III and IV, re-staging is recommended after 2 to 4 cycles. Responding cases are allowed to continue treatment or to be included in clinical trials

Anthracyclines (or anthracycline antibiotics) are a class of dugs described as being cell- cycle non specific chemotherapy. They have been used as efficacious antineoplastic agents for many haemopoietic (Lymphomas. Leukemias) and solid cancers as in breast cancer. **(Minotti, 2004).**

The heart is especially susceptible to anthracycline-induced damage, in part, owing to anthracyclines' high affinity for cardiolipin**. (Pointon et al, 2010)**

Prophylactic use of antihypertensives to prevent anthracycline-induced cardiomyopathy has been utilized in several studies.

This is a prospective randomized pilot trial including 50 patients of presented at Kasr Al Ainy clinical oncology department during the period May 2013 till September 2014.

AIM OF WORK

- Assessment of the prognostic value of early introduction of second line chemotherapy (ESHAP +/- R).
- Assessment of the effect of prophylactic antihypertensives on the incidence of anthracycline-induced Cardiomyopathy is a second endpoint.

CHAPTER I

Introduction to DLBCL

Diffuse large B-cell lymphoma (DLBCL) is the most common type of non-Hodgkin lymphoma (NHL) in the world, and accounts for 30%–40% of all adult NHLs. The 2008 WHO classification of lymphomas described more than 15 DLBCL subgroups based on distinct morphologic, biologic, immunophenotypic, and clinical parameters. Although potentially curable, 40% of patients with DLBCL will die of relapsed or refractory disease. The standard of care for initial treatment of DLBCL is rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone on a 21-day schedule (R-CHOP21) for six cycles. **(Vaidya and Witzig, 2014)**

Epidemiology of DLBCL

Incidence

NHL was ranked as the fifth most frequent cancer in Egypt (estimated using the results of the National Population-Based Registry Program of Egypt 2008–2011 and published in September 2014) accounting for 4.6%. It represents the fourth most common type of cancers in males and accounts for 5.4 % of all cancers in males, while in females it accounts for 3.8% of all cancers (fifth most common). **(Ibrahim et al., 2014)**

Table (1): The most frequent cancers in Egypt estimated using the results of the National Population-Based Registry Program of Egypt 2008–2011. (Amal S. Ibrahim et al., 2014)

Site	%	Crude rate	ASR
Males			
Non-Hodgkin lymphoma	5.48	6.4	10.4
Females			
Non-Hodgkin lymphoma	3.80	4.2	6.1
Both Sexes			
Non-Hodgkin lymphoma	4.64	5.4	7.5

Aetiological factors

The cause of most cases of NHL is unknown, although several genetic diseases, environmental agents, and infectious agents have been associated with the development of lymphoma. **(Jonathan et al., 2012)**

Immunosuppression:

a- Conginetal

Several rare inherited immunodeficiency states are associated with as much as a 25% risk of developing lymphoma. As severe combined immunodeficiency, hypogammaglobulinemia, common variable immunodeficiency, Wiskott-Aldrich syndrome, and ataxia-telangiectasia and they are often associated with EpsteinBarr virus (EBV) and vary in appearance from initial polyclonal B-cell hyperplasia to monoclonal lymphomas**. (Gaidano et al., 1998)**

b- Acquired:

As in AIDS and after solid organ transplantation . Also, in patients with a variety of autoimmune disorders, including rheumatoid arthritis, psoriasis,and Sjogren syndrome. **(Jonathan et al.,2012)**

Infections:

a- Bacterial

There is a relationship between Borrelia burgdorferi and primary cutaneous B-cell lymphoma confirmed after demonstration of the organism in lesional skin of patients with this lymphoma, presumably implicating chronic antigen stimulation in the skin in response to B. burgdorferi infection. **(Jonathan et al., 2012)**

b-Viral

Hepatitis C virus (HCV):

Several epidemiological studies have been conducted since 1990s to investigate the link between HCV and NHL .Studies revealed increased risk of B cell NHL in countries with high prevalence of HCV infection such as Italy, Egypt **(Goldmann et al, 2009)** and Japan ,while in countries with low prevalence of HCV infection ,no association was evident**. (Collier et al., 1999).**

A meta-analysis in 2003 ,Forty-eight studies (5542 patients) were evaluated . The mean HCV infection prevalence was 13% (95% CI: 12%-14%), Ten studies compared HCV prevalence in B-NHL (17%) and healthy controls (1.5%) (OR: 10.8; 95% CI: 7.4-16). **(Gisbert et al, 2003)**

Results from the US Surveillance ,Epidemiology and End Results (SEER) – Medicare data base ,61,464 cases were selected and HCV was

associated with increased risk of DLBCL (OR 1.5), MZL(OR 2.2), Burkitt's lymphoma (OR 5.2) and follicular lymphoma (OR 1.88**). (Anderson et al., 2008).**

Diffuse large B cell lymphoma and marginal zone lymphomas are the histotypes most frequently associated with HCV infection .Many mechanisms have been proposed for explaining HCV-induced lymphoproliferation; the role of HCV infection in lymphogenesis may be related to the chronic antigenic stimulation of B cell response. similarily chronic HCV infection may possibly sustain a multi-step evolution to overt low grade lymphoma into high grade non Hodgkin lymphoma. Independence from antigenic stimulation can occur at this step due to additional genetic aberrations. **(Marcucci and Mele, 2013)**

Also, it has been hypothesized the HCV antigens such as NS3 may be involved in the induction of lymphoma. In addition envelope protein such as E2protein can play a role in lymphagenesis; it interacts with the tetraspanin CD81, present on B cell surface, lowering the threshold and leading to a polyclonal B cell activation. **(Pileri et al ,1998).** The specific immunoglobulin also binds the E2 protein as a human anti –E2 antibody**. (Quinn et al, 2001).**