Management outcome of malignant lymphoproliferative disorders in hepatitis C virus infected patients

Thesis

Submitted for partial fulfillment for the requirement of master degree in clinical hematology

By

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2015

Acknowledgment

First and foremost ((Thanks to Great Allah)) the most merciful and kind.

It is a pleasure to express my deepest thanks and profound respect to Dr. Mohammed Roshdy al Masry Professor of internal medicine department of hematology faculty of medicine Cairo University for his continuous encouragement and valuable supervision throughout this work.

Special thanks to Dr. Manal El Husseiny Abo Farha professor of internal medicine department of hematology faculty of medicine Cairo University.

Also I would like to express my gratitude to Dr. Nehad Mohammed Tawfik, assistant professor of internal medicine department of hematology faculty of medicine Cairo University.

Words fail to express my deep appreciation to my family for their continuous help, support and encouragement as without their help, this work never be completed.

To my elder brother Mohammed, your support has made me a stronger person and I will forever be grateful.

ABSTRACT

Viral hepatitis C is a major public health problem in Egypt with high prevalence of sero-positivity. As a lymphotropic virus, HCV is expected to be responsible for the lymphoproliferative disorders discovered in chronic patients either benign as autoimmune conditions or malignant expansions in B-Cell clones. The number of patients suffering from malignant lymphoproliferative disorders on top of HCV infection is rising as well. This retrospective study will address the clinical progress and management outcome in LPD patients with hepatitis C virus compared to patients with similar disease status but without HCV infection. The study will be carried on 96 patients in two pair-matched groups of patients with malignant lymphoproliferative disorders (HCV vs Control).

Keywords: DLBCL, Hepatitis C virus, CLL.

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List of Abbreviation

AID	Activation-induced cytidine deaminase
AIHA	Autoimmune hemolytic anemia
ALK1	Anaplastic lymphoma kinase
ALPS	Autoimmune lymphoproliferative syndrome
ALT	Alanine aminotransferase
ANCOVA	Analysis of covariance
Ara c	Arabinosylcytosine
ASCT	Autologous stem cell transplantation
AST	Aspartate aminotransferase
Auc	Area under the curve
B-CLPDs	B-cell chronic lymphoproliferative disorders
BAFF	B-cell activating factor
BCA-1	B-cell-attracting chemokine-1
Bcl-2	B cell lymphoma 2
BCR	B cell receptor
Blc	B-lymphocyte chemoattractant
BLyS	B lymphocyte stimulator
BM	Bone marrow
CBC	Complete blood count
CD	Cluster of differentiation
CDC	Centers for Disease Control and Prevention
CDR3	Complementarity determining region 3
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CHS	Chediak – Higashi syndrome
CLL	Chronic lymphocytic leukemia
CNS	Central nervous system
CODOX-M	Cyclophosphamide, vincristine, doxorubicin, high-dose methotrexate

CR	Complete remission
CT	Computed tomography
CVAD	Cyclophosphamide, vincristine, Adriamycin, and dexamethasone
CVP	Cyclophosphamide, vincristine, and prednisone
CXCL13	Chemokine (C-X-C motif) ligand 13
Del	Deletion
DHAP	Dexamethasone, high dose Ara C, also known as cytarabine and cisplatin
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
EBER	Epstein-Barr virus encoded RNA
EBV	Epstein-Barr virus
EFS	Event-free survival
EIA	Enzyme immune assay
ELISA	Enzyme-linked immunosorbent assay
EPOCH	Etoposide, vincristine, doxorubicin, cyclophosphamide, and prednisone
ESHAP	Etoposide, methylprednisolone (solumedrol), high-dose cytarabine (ara-C) and cisplatin
FCM	Fludarabine, cyclophosphamide, and mitoxantrone
FCM	Fludarabine, cyclophosphamide, and mitoxantrone
FCR	Fludarabine, cyclophosphamide, and rituximab
FDA	Food and Drug Administration
FISH	Fluorescence in situ hybridization
FL	Follicular lymphoma
FLC	Free light chain
GELA	Group d'Etude des Lymphomas de l'Adulte
GEMOX	Gemcitabine, oxaliplatin
GI	Gastrointestinal
GPD	Gemcitabine, dexamethasone, and cisplatin
GSF	Granulocyte-stimulating factor
GY	Gray unit

HBV	Hepatitis B virus
HCC	Hepatocellular carcinoma
HCL	Hairy cell leukemia
HCV	Hepatitis C virus
HDT	High dose therapy
HIV	Human immunodeficiency virus
HL	Hodgkin lymphoma
HLA	Human leukocyte antigen
HTLV-1+	Human T-cell leukemia virus type 1
ICE	Ifosfamide, carboplatin, etoposide
IFN	Interferon
Ig	Immunoglobulin
IgD	Immunoglobulin D
IGEV	Ifosfamide, gemcitabine, and vinorelbine
IgH	Immunoglobulin heavy chain
IgM	Immunoglobulin M
IPI	International Prognostic Index
IPT	Immunophenotyping
IT	Intrathecal
IVDA	Intravenous drug abused
KSHV	Kaposi sarcoma–associated herpesvirus
LDH	Lactate dehydrogenase
LFT	Liver function test
m RNA	Messenger RNA
MALT	Mucosa associated lymphoid tissue
MC	Mixed crioglobulinemia
MGUS	Monoclonal gammopathy of undetermined significance
MHC	Major histocompatibility complex
Mip 1alpha	Macrophage inflammatory protein 1 alpha
MiRNA	Micro RNA
MPS	Methylprednisolone
MRD	Minimal residual disease
MRI	Magnetic resonance imaging
MTX	Methotrexate

NHLs	Non-Hodgkin lymphomas
NK	Natural killer cells
NPM	Nucleophosmin
NS	Nonstructural
OLT	Orthotopic liver transplantation
OPN	Osteopontin
OR	Odd ratio
ORR	Overall response rate
OS	Overall survival
PBMCs	Peripheral blood mononuclear cells
PCR	Pentostatin, cyclophosphamide, and rituximab
PCR	Polymerase chain reaction
PEG	Polyethylene glycol
PET	Positron emission tomography
PFS	Progression free survival
PLL	Prolymphocytic leukemia
PO	Per os, by mouth or orally
PS	Performance state
PTLD	Post-transplant lymphoproliferative disorder
R CHOP	Rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone
R-CVP	Rituximab, cyclophosphamide, vincristine, and prednisone
REAL	Revised European American Lymphoma
RF	Rheumatoid factor
RFLPs	Restriction fragment length polymorphisms
RFT	Renal function test
RR	Response rate
RT	Radiotherapy
SF3B1	Splicing factor 3b
SLL	Small lymphocytic lymphoma
SMZLs	Splenic marginal zone lymphomas
SVR	Sustained virologic response
TB	Tuberculosis
TMA	Transcription-mediated amplification

TNF	Tumor necrosis factors
UTR	Untranslated region
VDJ	Variable, diversity, joining gene segment
WAS	Wiskott –Aldrich syndrome
WHO	The World Health Organization
ZAP-70	Zeta-chain-associated protein kinase 70

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INTRODUCTION

A number of epidemiologic studies have demonstrated an association between non-Hodgkin's lymphoma (NHL) and hepatitis C virus (HCV) infection, suggesting that HCV plays a role in the development of NHL **(Mele et al, 2003).**

Low-grade marginal zone lymphoma has been the lymphoma subtype most commonly associated with HCV-infection, while limited data are available regarding HCV-positive patients with diffuse large B-cell lymphoma (DLBCL) **(Hartridge-Lambert et al, 2012).**

Clinicopathological characteristics at presentation, tolerance to chemotherapy, natural history and clinical outcome of patients with HCV-positive DLBCL are still unclear. This is due to the heterogeneity in histology and treatment strategies for DLBCL with HCV infection and a lack of data based on large series of unselected patients **(Ennishi et al, 2010).**

Previous studies involving lymphoma patients with HCV infection have shown good tolerance to standard chemotherapy (i.e., cyclophosphamide, doxorubicin, vincristine and prednisone (CHOP) regimens **(Kawatani et al, 2001).**

However, these studies were mainly conducted before the use of rituximab in DLBCL patients. On the other hand, there are several

reports that DLBCL patients with HCV infection may exhibit a characteristic clinical presentation, poor tolerance to intensive chemotherapy and poorer survival **(Arcaini et al, 2009).**

AIM OF THE WORK

The aim of our study to compare outcome of management of lymphoproliferative disease in HCV infected versus non-HCV infected patients.

CHRONIC LYMPOPROLIFERATIVE DISORDERS

Chronic lymphoproliferative disorders are a heterogeneous group of malignant clonal proliferation of lymphocytes. They are classified as sub-types of non-Hodgkin's lymphoma and include disorders of B, T and NK-cell lineages all of which are further classified as distinct entities. Chronic B-cell lymphoproliferative disorders are much more common and in general have an indolent clinical course **(Mahima et al, 2010).**

B-cell chronic lymphoproliferative disorders (B-CLPDs) result from the proliferation and accumulation of mature-appearing aberrant B-lymphocytes arrested at a given stage of differentiation**.** B-CLPDs are generally believed to result from the monoclonal expansion of a single transformed B lymphocyte. Therefore, the B lymphocytes constitute a clone in which all cells are related by possessing the original transforming mutation, possessing identical VDJ rearrangements of the immunoglobulin heavy chain (IgH) gene, and showing restricted immunoglobulin (Ig) light chain expression. Additionally, distinctive genetic and phenotypic features may be gained during the evolution of the disease. In this sense, the presence of 2 or more morphologically different populations of neoplastic lymphocytes in the same patient, detected either simultaneously or at different time points, is usually interpreted as reflecting either different maturation stages or sub clone formation within the original malignant tumor stem cell line **(Orfao et al, 2003).**