Randomized Study of Rituximab-ICE versus Gemcitabine, Methylprednisolone, and Cisplatin in Patients with Recurrent / Refractory CD20+ Diffuse Large B-Cell Lymphoma (DLBCL)

Thesis

Submitted For Partial Fulfillment of MD Degree in Oncology & Nuclear Medicine

Presented By

Esaam Sameir Ahmad
M.B.B.Ch, M.Sc.

Supervised By

Prof. Dr. Salwa Massoud Ibrahim
Professor of clinical Oncology & nuclear Medicine
Faculty of Medicine, Ain Shams University

Prof. Dr. Mostafa Mahmoud Nassaar
Professor of Hematology/Oncology
Al-Maadi Military Hospital

Prof. Dr. Nevine Mahmoud Gado
Professor of clinical Oncology & nuclear Medicine
Faculty of Medicine, Ain Shams University

Prof. Dr. Mohammad Esaam Saleh
Professor of clinical Oncology & nuclear Medicine
Faculty of Medicine, Ain Shams University

Faculty of Medicine
Ain Shams University
2012

Acknowledgement

All praise is due to Allah, and may His peace and blessings be upon the Prophet.

My words stand short of my supreme gratitude and thanks to Prof. Dr. Salwa Masood, professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shames University (may God have mercy on her) and to Prof. Dr. Nevine Mahmoud Gado, professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shames University, for her continuous supervision, generous encouragement, moral support, kindness & guidance from the very early stage of this research as well as giving me extraordinary experiences throughout the work.

Special thanks are due to Prof. Dr. Mostafa Mahmoud Nassaar, Professor of Hematology/Oncology, Al-Maadi Military Hospital, and Prof. Dr. Mohammad Esaam Saleh, Professor of Clinical Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shames University, for dedicating so much of their precious time and effort, and for their honest and constant guidance to complete this work, words of thanks are so little for their great help in preparation of this work.

Esaam Samier

Contents

List of Abbreviations

aa IPI	Age-adjusted IPI
AITL	Angioimmunoblastic T-cell Lymphoma
AJCC	American Joint Committee on Cancer
ALCL	Anaplastic Large Cell Lymphoma
ALL	Acute Lymphoblastic Leukemia
APCs	Antigen-Presenting Cells
ASCOD	Ain Shams University Clinical Oncology Department.
ASCT	Autologous Stem Cell Transportation
ATLL	Adult T-Cell Lymphoma/Leukemia
BL	Burkitt's Lymphoma
BLL	Burkitt's-Like Lymphoma
CD	Cluster of Discrimination
CDC	Complement-Dependent Cytotoxicity
CHOP	Cyclophosphamide+Hydroxydaunorubicin+Oncovine+Prednisone
CLL	Chronic Lymphocytic Leukemia
CNS	Central Nervous System
CR	Complete Remission
CSF	Cerebro-Spinal Fluid
DFS	Disease-Free Survival
DLBCL	Diffuse Large B-Cell Lymphoma
DNA	Deoxyribonucleic Acid
EBV	Ebestein Bar Virus
ECOG	Eastern Co-Operative Oncology Group (USA)
EN	Extra-Nodal
EORTC	European Organization For Research And Treatment Of Cancer
ESMO	European Society For Medical Oncology
FISH	Fluorescence *In Situ* Hybridization
FL	Follicular Lymphoma
G-CSF	Granulocyte-Colony Stimulating Factor
GELA	Groupe D'étude Des Lymphomes De l'Adulte (France)
GIT	Gastro-Intestinal Tract
HDT/ ASCT	High-Dose Chemotherapy Followed By ASCT
HIV	Human Immune-Deficiency Virus
HL	Hodgkin's Lymphoma
HLA	Human Leukocyte Antigen
IFRT	Involved-Field Radiotherapy
Ig	Immunoglobulin
IHC	Immunohistochemistry
IPT	Immunophenotyping
IPI	International Prognostic Index
LDH	Lactate Dehydrogenase
LCL	Large Cell Lymphoma
LPL/WM	Lymphoplasmacytic Lymphoma / Waldenström Macroglobulinemia
MALT	Mucosa-Associated Lymphoid Tissue
MCL	Mantle Cell Lymphoma
MRI	Magnetic Resonance Imaging
MTA	Molecular Targeted Agent
MZL	Marginal Zone Lymphoma
NCI	National Cancer Institute
NEMROCK	Kasr Al-Aini Center Of Clinical Oncology, Cairo University, Egypt
NHL	Non-Hodgkin's Lymphoma
OS	Overall Survival
PET	Positron Emission Tomography
PFS	Progression-Free Survival

PMBC L	Primary Mediastinal Large B-Cell Lymphoma (A Subtype Of DLBCL)
PNP	Peripheral Neuropathy
PR	Partial Remission
PTCL	Peripheral T-Cell Lymphoma
QLQ	Quality Of Life Questionnaire
REAL	Revised European American Classification Of Lymphoid Neoplasms (1994)
RTOG	Radiation Therapy Oncology Group
RT	Radiation Therapy
SWOG	South-West Oncology Group (USA)
UICC	Union For International Cancer Control
WF	Working Formulation (1982)
WHO	World Health Organization

List of Tables

List of Figures

INTRODUCTION

The Non-Hodgkin's Lymphomas (NHLs) are a group of entities that vary in clinical behavior and morphologic appearance. The various types of NHLs are thought to represent neoplastic lymphoid cells that are arrested at different stages of normal differentiation. On the basis of their natural history, NHLs can be clinically classified as indolent, aggressive or highly aggressive **(Martin E et al, 2005)**.

There were an estimated 356 000 new cases of NHL and 192 000 deaths from NHL worldwide in 2008 **(Burton C Et al, 2010).**

Two complementary classification systems for NHL are used, the Working Formulation (WF) and the World Health Organization (WHO) classification**,** which was based on the Revised European American Lymphoma (REAL) classification. The WF satisfactory captures and describes the most common lymphomas. The REAL/WHO classifications intend to correlate lymphoma entities with the normal lymphocyte counterpart and are more applicable to the uncommon lymphomas. Because of its dependence on immunophenotypic and cell lineage analysis, the REAL/WHO system is more reproducible **(Dennis A et al, 2009).**

Diffuse large B-cell lymphoma (DLBCL) was the most common lymphoma in the international study of the REAL, accounting for 31% of the cases. DLBCLs express one or more B-cell associated antigens (CD19, CD20, CD22, and CD79a), as well as CD45, and often but not always, surface Ig. They may coexpress CD5 or CD10 **(Fisher R et al, 2005).**

Approximately 40-60% of patients with aggressive non-Hodgkin lymphoma (NHL) treated with standard anthracycline-based regimens either fail to achieve a complete response (CR) or relapse after attaining a CR **(Fisher R et al, 1993).** High-dose chemotherapy with autologous stem cell transplantation (ASCT) can be

curative in a proportion of patients with relapsed or primary refractory disease provided that a CR or partial response (PR) can be induced with second-line chemotherapy **(Vose et al, 2001).**

The Rituxan® (Rituximab) antibody is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. The antibody is an IgG1 kappa immunoglobulin containing murine light and heavy chain variable region sequences and human constant region sequences. Rituximab is composed of two heavy chains of 451 amino acids and two light chains of 213 amino acids (based on cDNA analysis) and has an approximate molecular weight of 145 kD. Rituximab has a binding affinity for the CD20 antigen of approximately 8.0 nM.

Rituximab binds specifically to the antigen CD20 (human B-lymphocyte-restricted differentiation antigen, Bp35), a hydrophobic transmembrane protein with a molecular weight of approximately 35 kD located on pre-B and mature B lymphocytes **(Valentine et al,1989)**. The antigen is also expressed on >90% of B-cell non-Hodgkin's lymphomas (NHL) **(Anderson et al,1984)** , but is not found on hematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissues**.** CD20 regulates an early step(s) in the activation process for cell cycle initiation and differentiation**,** and possibly functions as a calcium ion channel **(Tedder et al, 1990).** CD20 is not shed from the cell surface and does not internalize upon antibody binding **(Press et al, 1987).** Free CD20 antigen is not found in the circulation **(Einfeld DA et al, 1988).**

Despite advances in the management of aggressive non-Hodgkin's lymphoma, the treatment of relapsed and primary refractory disease remains a major challenge. High-dose chemotherapy or radio-chemotherapy followed by autologous or allogeneic stem cell transplantation (SCT) is a potentially curative treatment approach; however, the applicability of this approach is restricted to patients responding to second-line chemotherapy. Thus, second-line therapy must be both

efficacious and without stem cell or organ toxicity that would compromise the ability to proceed to SCT. The ifosfamide, carboplatin and etoposide (ICE) regimen was developed to address these challenges. In a series of prospective clinical trials, 222 patients were treated with the ICE regimen, with an overall response rate of 72%. The mobilization of stem cells with this regimen was excellent, with 86% of patients mobilizing at least 2.0 x 10^6 CD34+ cells/kg. Rituximab was subsequently added to the ICE regimen for patients with diffuse large B-cell lymphoma (DLBCL) to improve upon these favorable results. This resulted in an increased complete remission rate **(Zelenetz AD et al, 2003).**

There is currently no standard salvage chemotherapy regimen in relapsed and refractory lymphoma. Gemcitabine is a nucleoside analogue, which acts synergistically with cisplatin both in vitro and in clinical studies. The combination of gemcitabine, cisplatin and methylprednisolone (GEM-P) was evaluated in 41 heavily pretreated patients with relapsed and refractory Hodgkin's and non-Hodgkin's lymphoma. The best-achieved response rate (RR) was 79% (95% CI), with a complete RR of 21%. In patients with chemo-resistant disease, the RR was 63%. Myelosuppression was the main toxicity, the incidence of Grade 3 or 4 anemia, neutropenia and thrombocytopenia was 17.1, 61.0 and 53.7% respectively. Only one patient had neutropenic sepsis and none of the patients suffered from hemorrhage. Grade 3 or 4 nonhaematological toxicity was minimal and stem cell mobilization was not inhibited **(Ng M et al, 2005).**

Clinical trial was designed to assess the efficacy and safety of gemcitabine, cisplatin and methylprednisolone (GEM-P) for patients with relapsed or refractory Hodgkin's disease (HD) and non-Hodgkin's lymphoma. Twenty-one patients were treated with gemcitabine, cisplatin and methylprednisolone. Of these, 20 patients were evaluable for response. The median age was 38 years (range 17-64 years). Histological subtypes were: nodular sclerosing HD (n = 10), diffuse large B cell (n = 5), T cell-rich B cell (n = 2), follicular (n = 2), mantle cell (n = 1) and

enteropathy-associated T-cell lymphoma (n = 1). The median remission duration prior to receiving GEM-P was only 42 d. The overall objective response rate was 80% [95% confidence interval (CI): 56-94%], including five complete and 11 partial responses. GEM-P induced responses in all histological subtypes, primary progressive disease and patients who had received a previous autograft. The only grade 3-4 toxicity was myelosuppression. However, no cases of febrile neutropenia or hemorrhage with thrombocytopenia were encountered. Median survival has not yet been reached and survival probability at 1 year was 60.8% (95% CI: 31.9-80.5%) **(Chau I et al, 2003).**

Aim of Work

- To assess the antitumour efficacy and tolerability following two regimens of chemotherapy in refractory / relapsed DLBCL patients; arm A: R-ICE regimen and arm B: GEM-P.
- Comparative study including response rate, survival rate and toxicity will be done.

EPIDEMIOLOGY OF NHL

International Non-Hodgkin's Lymphoma (NHL) incidence rates vary as much as fivefold. The highest reported incidence rates are in the United States, and also Europe and Australia; the lowest rates have generally been reported in Asia **(Jemal A et al, 2004).** There were an estimated 356 000 new cases of NHL and 192 000 deaths from NHL worldwide in 2008 **(Burton C et al, 2010)**. The NHLs and Hodgkin's disease are the most commonly occurring hematologic malignancies in the United States. They now represent 4% to 5% of all new cancer cases and are the fifth leading cause of cancer death in the United States and the second fastest growing cancer in terms of mortality **(Kevin K et al, 2010).**

An increasing NHL incidence at a rate of 3-4% per year was observed for the 1970s and 1980s. This stabilized in the 1990s, nevertheless still with an annual rise of 1-2%, resulting in almost a doubling of the NHL incidence. This rise has been noted worldwide, particularly in elderly persons > 55 years. Concerning gender subgroups, a male predominance throughout all age groups is apparent. Although the NHL incidence has historically been higher in whites than blacks, disproportional increase has recently been observed in the latter group. Increase in high-grade NHL and extranodal disease are predominant. Differences in geographic distribution are striking for follicular lymphoma, which is more common in Western countries than elsewhere. Asians have higher rates of aggressive NHL, T-cell lymphomas, and extranodal disease **(Muller AM, 2005).**

Diffuse large B-cell lymphoma (DLBL, DLBCL, or DLCL) is a type of aggressive non-Hodgkin lymphoma. It accounts for approximately 40% of lymphomas among adults. The median age at diagnosis is 70 years, but it also occurs in children and young adults. As with most non-Hodgkin lymphomas, there is a male predominance, although primary cutaneous diffuse large B cell lymphoma is more common in women **(Mary Louise, 2005).**

In USA, From 2000-2004, the median age at diagnosis for non-Hodgkin lymphoma was 67 years of age. Approximately 1.7% were diagnosed under age 20; 4.2% between 20 and 34; 7.7% between 35 and 44; 14.1% between 45 and 54; 18.1% between 55 and 64; 22.6% between 65 and 74; 23.5% between 75 and 84; and 8.2% 85+ years of age. The age-adjusted incidence rate was 19.3 per 100,000 men and women per year. These rates are based on cases diagnosed in 2000-2004 from 17 Surveillance, Epidemiology and End Results (SEER) geographic areas **(table 1) (Ries et al, 2004).**

From 2000-2004, the median age at death for non-Hodgkin lymphoma was 74 years of age. Approximately 0.5% died under age 20; 1.7% between 20 and 34; 3.1% between 35 and 44; 7.4% between 45 and 54; 13.9% between 55 and 64; 23.7% between 65 and 74; 33.4% between 75 and 84; and 16.3% 85+ years of age. The age-adjusted death rate was 7.6 per 100,000 men and women per year. These rates are based on patients who died in 2000-2004 in the US **(table 2) (Ries et al, 2004).**

Incidence Rates by Race In USA		
Race/Ethnicity	**Male**	**Female**
All Races	23.2 per 100,000 men	16.3 per 100,000 women
White	24.1 per 100,000 men	17.0 per 100,000 women
Black	18.1 per 100,000 men	11.9 per 100,000 women
Asian/Pacific Islander	15.7 per 100,000 men	11.2 per 100,000 women
American Indian/Alaska Native	11.6 per 100,000 men	9.5 per 100,000 women
Hispanic	19.2 per 100,000 men	14.2 per 100,000 women

Table (1) Incidence Rates by Race In USA

(Adapted from Ries et al, 2004)

In the Middle East, high rates of intestinal extranodal disease are observed, whereas in Africa, endemic Burkitt's lymphoma accounts for a substantial proportion. Risks for developing NHL include immunosuppression and a causal link between infectious agents, and lymphomagenesis has also been determined, particularly for human T-cell leukemia/lymphoma virus type 1 (HTLV-1), Epstein-Barr virus (EBV), and Helicobacter pylori infections. Exposures to environmental agents and occupational risks have been studied; however, their significance is as yet uncertain **(Muller AM, 2005).**

Death Rates by Race In USA		
Race/Ethnicity	**Male**	**Female**
All Races	9.6 per 100,000 men	6.2 per 100,000 women
White	9.9 per 100,000 men	6.4 per 100,000 women
Black	6.5 per 100,000 men	4.3 per 100,000 women
Asian/Pacific Islander	5.8 per 100,000 men	3.9 per 100,000 women
American Indian/Alaska Native	6.1 per 100,000 men	5.0 per 100,000 women
Hispanic	6.9 per 100,000 men	4.8 per 100,000 women

Table (2) Death Rates by Race In USA

(Adapted from Ries et al, 2004)

In Egypt, malignant lymphomas are relatively common. The exact national incidence is not precisely known due to absence of a National Cancer Registry and the only data available are from hospital registries. At Ain Shams Radiation Oncology and Nuclear Medicine Department (RONMD), the total number of cancer cases in three years (from 2004 to 2006) was 4046 cases, with 413 lymphoma cases constituting 10.2% of cases. Relative predominance of NHL over HD was at a rate of 2:1 **(Ibrahim, et al 2008).**