Gemcitabine, Dexamethasone, And Cisplatin (GDP) Versus Dexamethasone, Cytarabine, And Cisplatin (DHAP) As Salvage Chemotherapy For Patients With Relapsed Or Refractory Non-Hodgkin's Lymphoma

Thesis

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By

Nawal Eltohamy Mohamed
(M.B.B.Ch., M.Sc.)
Faculty of Medicine, Ain Shams University

Supervised by

Prof. Soheir Sayed Ismaeil
Professor and chief of department of Oncology & Nuclear medicine
Faculty of medicine
Ain shams university

Prof. Tarek Hussein Kamel
Professor of Oncology & Nuclear medicine
Faculty of medicine
Ain shams university

Dr. Mohamed Yassin Mustafa
Lecturer of Oncology & Nuclear medicine
Faculty of medicine
Ain shams university

Faculty of medicine
Ain Shams University

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الطبيبة/ نوال التهامي محمد

ماچستير علاج الأورام و الطب النووي
جامعة عين شمس

تحت إشراف

الدكتورة/ سهير سيد إسماعيل

أستاذ و رئيس قسم علاج الأورام و الطب النووي
كلية الطب- جامعة عين شمس

الدكتور/ طارق حسين كامل

أستاذ علاج الأورام و الطب النووي
كلية الطب - جامعة عين شمس

الدكتور/ محمد يس مصطفى

مدرس علاج الأورام و الطب النووي
كلية الطب - جامعة عين شمس

كلية الطب

جامعة عين شمس

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List of abbreviations

ABC	Activated B Cell
ADL	Activities of daily living
AIDS	The acquired immune deficiency syndrome
ALK1	Anaplastic lymphoma kinase gene
ASCT	Autologous Stem cell transplantation
ATLL	Adult T-cell leukemia/lymphoma
BC	British Columbia
Bcl	B-cell lymphoma 2
BCR	B-cell receptor
BSA	Body surface area
CD	Cluster of differentiation
CNS	Central nervous system
CORAL	Collaborative Trial in Relapsed Aggressive Lymphoma
CR	Complete response
CSF	Cerebrospinal fluid
CT	Computed tomography
DLBCL	Diffuse large B cell lymphoma
DNA	Deoxyribonucleic acid
EBV	Epstein–Barr virus
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
FDG	18F-deoxyglucose
FFS	Failure-free survival
FISH	Fluorescence in situ hybridization
FNA	Fine needle aspiration
GCB	Germinal center B Cell
GE/TAMO	Grupo Español de Linfomas/ Trasplante Autólogo de Médusa ósea’
GELA	Groupe d'Etude des Lymphomes de l'Adulte
GEP	Gene expression profiling

GLSG	German Lymphoma Study Group
GY	Gray
HAART	Highly active antiretroviral therapy
HCV	Hepatitis C virus
HDT & SCT	high-dose therapy & Stem cell transplantation
HHV-8	Human herpes virus 8
HOVON	Hemato-Oncologie voor Volwassennen Nederland
HTLV-1	Human T-cell lymphotropic virus type 1
IARC	International Agency for Research on Cancer
IFRT	Involved-field RT
Ig	Immunoglobulin
IPI	International Prognostic Index
IVLBL	Intravascular Large B Cell Lymphoma
IWG	International Working Group
KSHV	Kaposi's sarcoma–associated herpes virus
LDH	lactate dehydrogenase
MALT	Mucosa-associated lymphoid tissue
MCL	Mantle cell lymphoma
MINT	Mabthera International Trial
MRI	Magnetic resonant imaging
MSKCC	Memorial Sloan-Kettering Cancer Center
MZLs	Marginal zone lymphomas
NCCN	National Comprehensive Cancer Network
NCI-CTC	Common Toxicity Criteria of the National Cancer Institute
NHLs	Non Hodgkin lymphomas
NOS	Not otherwise specified

NPM	Nucleophosmin gene
OS	Overall survival
PD	Progressive disease
PEL	Primary effusion lymphoma
PET	Positron emission tomography
PFS	Progression-free survival
PKCβ	Protein kinase C beta
PMBL	Primary Mediastinal Large B-Cell Lymphoma
PR	Partial remission
REAL	Revised European-American Lymphoma
RT	Radiation therapy
R-IPI	Revised IPI
SaaIpI	Secondary age-adjusted IPI
SD	Stable disease
SEER	Surveillance Epidemiology and End Results
SUV	Standard uptake values
SWOG	Southwest Oncology Group
Syk	Spleen tyrosine kinase
TTF	Time to treatment failure
UK	United Kingdom
US	United States
ULN	Upper limit of normal
WHO	World Health Organization

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Introduction

Non-Hodgkin's lymphoma (NHL) is the seventh most common cancer and is the ninth most common cause of cancer death in males and the sixth in females and it is the second fastest rising cancer in incidence and death rates in the United States (US). It is estimated that 65,980 men and women (35,990 men and 29,990 women) will be diagnosed and 19,500 men and women will die of non-Hodgkin lymphoma in 2009**.** The age-adjusted incidence rate was 19.5 per 100,000 per year and the age-adjusted death rate was 7.1 per 100,000 per year ***(Horner et al, 2009).***

It is interesting to note the high rates of NHL in Egyptians. The age-adjusted incidence rate for lymphoma among Egyptians was 16.3 per 100.000. This rate exceeded the US Surveillance Epidemiology and End Results (SEER) incidence rate 15.3 per 100.000, considered one of the highest in the world ***(Freedman et al, 2006).*** Several studies have reported the possible role of infectious agents in the etiology of NHL. ***Cowgill et al, (2004)*** reported in an Egyptian case-control study a statistically significant association of HCV RNA with NHL.

Non-Hodgkin's lymphomas (NHL) are a heterogeneous group of lymphoid malignancies that differ greatly in clinical presentation, prognosis, and response to therapy. Diffuse large B-cell lymphoma (DLBCL) is the most common histological subtype of NHL, accounting for approximately 30–45% of all cases ***(Bruce et al., 2008).***

Combination chemotherapy is the mainstay of treatment for patients with DLBCL. The realistic goal of induction therapy

for DLBCL is to cure the disease. In fact, almost half of the patients with DLBCL may be cured with conventional therapy. The most widely used combination for the treatment of DLBCL has been CHOP (cyclophosphamide, doxorubicin, vincristine, prednisone). For patients with advanced DLBCL, this combination produces an approximate 50% to 60% Complete Response (CR) rate. Results are significantly improved by the addition of the anti-CD antibody rituximab, so that R-CHOP has rapidly become the new standard ***(Pfreundschuh et al, 2006).***

Studies of stem cell transplantation (SCT) have been carried out in many varieties of NHL but primarily in DLBCL. The most widely accepted use of Stem Cell Transplantation/High-Dose Chemotherapy (HDC) is in the treatment of patients with DLBCL who have relapsed following initial CHOP or R-CHOP chemotherapy ***(Philip et al, 1995).***

Only about 1/3 of patients who achieve complete response go on to relapse. Relapse of DLBCL, if it occurs, will usually take place within the first 2 years after achieving remission. If the patient is still able to tolerate aggressive therapy, salvage chemotherapy is employed. At present, there is no standard salvage chemotherapy. Common regimens include ICE (ifosfamide, carboplatin and etoposide), DHAP (dexamethasone, cytarabine and cisplatin) and ESHAP (etoposide, methylprednisolone, cytarabine and cisplatin) ***(Bruce et al, 2008).***

Gemcitabine has been shown to have clinical activity against several tumors, including lymphomas. Preclinical studies of gemcitabine and cisplatin have demonstrated synergy