Outcome of Fludarabine and Cyclophosphamide as a First Line Treatment for Chronic Lymphocytic Leukemia Patients.

Thesis
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List of Abbreviations

Ad-CD154	Adenovirus vector encoding recombinant CD154
ADCC	Antibody-dependent cellular cytotoxicity
ALL	Acute lymphoblastic leukemia
ATL	Adult T-cell leukemia
β2m	β2 microglobulin
bFGF	basic fibroblastic growth factor
BM	Bone marrow
CALGB	Cancer and Leukemia Group B
CAP	Cyclophosphamide, adriamycin, and prednisone
CD	Cluster of differentiation
CDC	Complement-mediated cytotoxicity
CHOP	Cyclophosphamide, doxorubicin, vincristine, and prednisone
CLB	Chlorambucil
CLL	Chronic Lymphocytic Leukemia
CMV	Cytomegalovirus
CR	Complete response
CTL	Cytotoxic T lymphocytes
CVP	Cyclophosphamide, vincristine, and prednison
Cy	Cyclophosphamide
DiSC	Differential staining cytotoxicity
DNA	Deoxyribonucleic acid
EBV	Eptien Barr Virus
F	Female
FAFFAB	French-American-British Group
FC	Fludarabine/Cyclophosphamide
FISH	Fluorescence in situ hybridization
FITC	Fluorescine isothiocyanate
FL	Follicular lymphoma
Flu	Fludarabine
G6PD	Glucose 6-phosphate dehydrogenase
GVHD	graft-versus-host disease
h-lL-6	Human interleukin-6

HB	Hemoglobin
HCL	Hairy cell leukemia
HLA	Human leucocytic antigen
ICAM-1	Intracellular adhesion molecule-1
IgH	Immunoglobulin heavy chain
IgVH	Immunoglobulin heavy chain variant
IL	Interleukin
IWCLL	International Workshop on Chronic Lymphocytic Leukemia
κ	Kappa
λ	Lambda
LDH	Lactic acid dehydrogenase
LDT	Lymphocyte doubling time
LGL	Large granular lymphocytes leukemia
LI	Lymphocyte infiltration
LPL	Lymphoplasmacytic lymphoma
M	Male
mAbs	Monoclonal antibodies
MBCL	Monocytoid B-cell lymphoma
MCL	Mantle cell lymphoma
MHC	Major histocompatibility complex
mRNA	Massenger ribonucleic acid
NA	Not applicable
NCIWG	National Cancer Institute Working Group
NEUT	Neutrophils
NGFr	Nerve growth factor receptor
NHL	Non-Hodgkin's lymphoma
NK	Natural killer
No	Number
NR	Not reached
NR	Not reported
ORR	Overall response rate
OS	Overall survival
PARP	Poly-ADP-ribose polymerase
PB	Peripheral blood

PBCL	Polyclonal B-cell lymphocytosis
PCD	Programmed cell death
PCNA	Proliferating cell nuclear antigen
PCR	Polymerase chain reaction
PD	Progressive disease
PE	Phycoerythrin
PFS	Progression-free survival
PLL	Prolymphocytic leukemia
PLT	Platelets
PR-nod	Nodular partial response
PR	Partial response
RB	retinoblastoma
Ref	Reference
Ritux	Rituximab
RNA	Ribonucleic acid
SCT	Stem cell transplantation
SD	Stable disease
sIg	surface immunoglobulin
SLVL	Splenic lymphoma with villous lymphocytes
SMZL	Splenic marginal zone lymphoma
sVCAM-1	Soluble vascular cell adhesion molecule-1
TGF-beta	Transforming growth factor beta
TK	Tyrosine kinase
TNFα	Tumor necrosis factor α
TRAP	Tartrate resistant acid phosphatase
TSP-1	Thrombospondin-1
VAD	Vincristine, doxorubicin, and dexamethasone
VEGF	Vascular endothelial growth factor
WBC	White blood cells
WHO	World Health Organization
ZAP-70	Zeta-chain (T-cell receptor) associated protein kinase (70 kDa)

ABSTRACT

Introduction: Chronic lymphocytic leukemia (CLL) is a neoplastic disease characterized by the accumulation of small mature appearing lymphocytes in the blood, marrow, and lymphoid tissues. Fludarabine and cyclophosphamide is a highly active and well-tolerated regimen with an acceptable level of toxicity in patients with previously untreated CLL

Aim of the work: This study aimed at better definition and characterization of our newly diagnosed CLL patients regarding their clinical presentation, staging and evaluating the efficacy, response rate, factors affecting response, and toxicity of fludarabine and cyclophosphamide as a first-line treatment.

Materials and methods: Between January 2002 and December 2006, 31 adult patients presented to the medical oncology department, National Cancer Institute with previously untreated chronic lymphocytic leukemia treated with FC regimen were included in this study. Clinical and laboratory findings of these patients were assessed. Also response and toxicity to FC regimens and diseases-free and overall survivals were assessed.

Results: Complete clinical remission was achieved in 48.4% of patients, the overall response rate (ORR) was 64.5%, the mean overall survival was 35.4 months, and the median time to disease progression was 25 months.

Conclusion: This study indicates that the combination of fludarabine and cyclophosphamide is able to induce a high response rate with acceptable toxicity in newly diagnosed CLL patients

Key words: Chronic lymphocytic leukemia-Fludarabine-Cyclophosphamide.

INTRODUCTION and AIM OF THE WORK

Introduction

Chronic lymphocytic leukemia (CLL) is a neoplastic disease characterized by the accumulation of small mature appearing lymphocytes in the blood, marrow, and lymphoid tissues, treatment of CLL is moving from the era of watchful waiting and palliative treatment to an aggressive approach, with the new therapeutic end points of achieving a complete remission and minimal residual disease, using novel agents singly or in combination **(Rai, 1999).**

Patients with CLL can relapse even after aggressive therapy and autografts. It is commonly assumed that to prevent relapse the level of minimal residual disease (MRD) should be as low as possible. To evaluate MRD, highly sensitive quantitative assays are needed **(Pekova et al., 2005).**

Several phase III studies have firmly established fludarabine as the first -line treatment for symptomatic, untreated patients with CLL **(Rai et al., 1996; Johnson, et al., 1996; Leporrier et al., 1997).** It was found that fludarabine and cyclophosphamide is a highly active and well-tolerated regimen with an acceptable level of toxicity in patients with previously untreated CLL **(Flinn et al., 1998).**

Aim of the work

This study aimed at better definition and characterization of our newly diagnosed CLL patients regarding their clinical presentation, staging and evaluating the efficacy, response rate, factors affecting response, and toxicity of fludarabine and cyclophosphamide as a first-line treatment.

REVIEW OF LITERATURE

DEFINITION

Chronic lymphocytic leukemia (CLL) is a neoplastic disease characterized by the accumulation of small mature -appearing lymphocytes in the blood, marrow, and lymphoid tissues **(Ries et al., 2003)**.

Ambiguity still persists as to the minimal diagnostic criteria for CLL. All recommendations require that the lower limit of the lymphocyte count in the peripheral blood of patients with CLL is greater than 4 X 10^{9}/L (the upper limit of normal) and more than 25% lymphocytes in the bone marrow. Increases in lymphocytes in blood and bone marrow must be sustained to differentiate them from reactive lymphocytosis due to infections and other causes. In morphologic appearance, the lymphocytes should be predominantly mature to exclude other variants, such as PLL, HCL, and large granular lymphocyte **(Ries et al., 2003)**

CLL has an average incidence of 2.7 persons per 100.000 in the United States **(Diehl et al., 1999),** this incidence increased to 3.5 per 100.000 based on recent estimates. The risk of developing CLL increases progressively with age and is 2.8 times higher for older men than for older women **(Ries et al., 2003)**.

In **Egypt**, according to the National Cancer Institute (NCI), Cairo University hospital based registry; CLL constituted **0.53 %** out of 9082 cancer cases (48 CLL patients) and **7 %** out of 687 leukemia cases registered during the year **2006 (Cancer registry at NCI, 2006).**

ETIOLOGY

ENVIRONMENTAL FACTORS:

Environmental factors do not appear to play a role in the pathogenesis of B-cell CLL **(Redaellet al., 2004).**

HEREDITARY FACTORS

Although most cases of CLL are sporadic, multiple cases of CLL may be found within a single family. There are numerous reports of families with multiple members having B-cell CLL. First-degree relatives of patients with CLL are more than three times at risk for having this disorder or other lymphoid neoplasms than is the general population **(Houlston et al., 2003).**

Clinical Features

PATIENT POPULATION

At diagnosis, most patients are over 60 years of age, and 90% are over age 50. The disease is extremely rare in persons under 25 years of age. There is a 2:1 male to female incidence and prevalence of CLL **(Dighiero et al., 1991).**