Dedication

ALL MY LOVE TO MY

My mother, My father,
My wife, My daughter, ...

محمد عبدالحميد

2009

إهـــداء

كـل حبي وتقديري إلـــى

أسرتي

أمى وأبى ..زوجتى وابنتى و....

بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما علمتنا إنك أنت العليم الحكيم

صدق الله العظيم

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Management of Chronic myeloid leukemia In Pediatrics At Ain Shams University And National Cancer Institute In The Last decade 95-05

Thesis

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دراسة تقييمية لعلاج حالات سرطان الدم المزمن فى الأطفال فى العقد الأخير بمستشفى الأطفال بجامعة عين شمس والمعهد القومى للأورام

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Abstract

Background: the cause of chronic myeloid leukemia is a constitutively active BCR-ABL tyrosine kinase , It is a very rare disease in children, BMT is still the only curative therapy but TKI developed a new era in CML management. **Subject and methods**: this study was conducted on 98 children and adolescents diagnosed as CML during the period between January 1995 to December 2005 , in the Pediatric Hematology / Oncology Unit , Children Hospital , Ain Shams University , National Cancer Institute and Nasser Institute. We recorded the epidemiological features of the disease, symptoms, physical signs, peripheral blood and BM analysis at initial diagnosis, follow up patients till December 2008 was done, comparison between different TTT modalities was performed regarding OS,CHR,CR, duration till remission, duration till blast crisis, tolerance to therapy and outcome. **Results**: there was male preponderance with a ratio about 2:1 ,CML still extremely rare in very young children, >58% of patients were older than 10 years at diagnosis, an incidental diagnosis was made in 23.4% of patients with lower TLC and higher HB% than symptomatic group, about 6.1% of patients diagnosed in accelerated phase, 11.2% in blast crisis, the most common symptoms were athenia and symptoms related to splenomegaly ,imatinib and BMT were superior to other TTT modalities, imatinib was superior to BMT regarding outcome and toxicity profile. **Conclusion**: imatinib has to be regarded as standard of care first line TTT in pediatric CML but the long term outcome can not yet be assessed. On the other hand alloSCT holds the promise of cure but with definite toxicity and mortality.

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Contents

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List of abbreviations

ALL	Acute Lymphoblastic Leukemia
AML	Acute Myeloblastic Leukemia
ATP	adenosine triphosphate
BCM	below costal margin
BM	bone marrow
BCR	breakpoint cluster region
CBL	casitas B-lineage lymphoma protein
CNS	central nervous system
CML	chronic myelogenous leukemia
CML-CP	CML chronic phase
CCR	complete cytogenetic response
CHR	complete hematological response
CMR	Complete Molecular response
CR	complete remission
Ara-C	Cytarabine
EBMT	European Group for Blood and Marrow Transplantation
FISH	fluorescence in situ hybridization
FAK	focal adhesion kinase
GVHD	Gravt versus host disease
GRB2	growth factor receptor-bound protein 2
GDP	guanosine diphosphate
GTP	guanosine triphosphate
HLA	human leucocytic antigen
INF	interferon
JAK-STAT	Janus kinase-signal transducers and activators of Transcription .
LAP	Leukocyte Alkaline Phosphatase
LFT	liver function test
MCR	major cytogenetic response
MIU	million international unit
MRD	minimal residual disease
MAPKs	mitogen-activated protein kinase
MR	Mortality rate

-ve	negative
NAP	Neutrophil Alkaline Phosphatase
OS	Overall survival
PR	partial remission
PB	peripheral blood
Ph	Philadelphia chromosome
PI3K	phosphatidylinositol 3 kinase
+ve	positive
PC	probability of stem cell cycling
P145	protien of 145 kilo Dalton
P190	protien of 190 kilo Dalton
P210	protien of 210 kilo Dalton
RAS	rat sarcoma
Rb	retinoblastoma
RT-PCR	reverse transcription-polmerase chain reaction
SRC	rous sarcoma virus of chickens
Ser-Thr	serine-theronine
SHC	src homolology containing protein
SCT	stem cell transplantation
SRE	stimulated response element
IRIS	The International Randomized Study of Interferone and ST1571 .
TLC	total leucocytic count
TC-1	transcopalamin 1
T(9;22)	translocation between chromosomes 9 and 22
TKI	Tyrosine kinase inhibitors
WBC	white blood cells

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INTRODUCTION

Chronic myelogenous leukemia (CML) is a clonal myeloproliferative disorder that account for 2-3 % of all cases of childhood leukemia. About 99% of the cases are characterized by a specific translocation, t (9 ;22) (q 34 ;q 11), known as the Philadelphia chromosome. The disease has been associated with exposure to ionizing radiation but very few children with CML have a history of such exposure ***(Roy et al., 2006).***

The disease is characterized clinically by an initial chronic phase in which the malignant clone produces an elevated leucocytic count with a predominance of mature forms but with increased numbers of immature granulocytes. Spleen is often greatly enlarged, often resulting in pain in the left upper quadrant of the abdomen. in addition to leucocytosis , the blood counts may reveal mild anemia and thrombocytosis ***(Druker et al., 2001).***

The presenting symptoms of CML are entirely nonspecific and may include fever, fatigue, weight loss, and anorexia. Splenomegaly may also be present. The diagnosis is suggested by increased numbers of myeloid cells with differentiation to mature forms in the peripheral blood and