

Dedication

ALL MY LOVE TO MY



*My mother, My father,
My wife, My daughter,*

محمد عبد الحميد

2009

إهداء كل حبي وتقديري إلى أسرتي



أمی وأبی ..زوجتی وابنتی و....

بسم الله الرحمن الرحيم

قَالُوا سُبْحَانَكَ لَا عِلْمَ
لَنَا إِلَّا مَا عَلَّمْتَنَا إِنَّكَ
أَنْتَ الْعَلِيمُ الْحَكِيمُ

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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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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