Outcome of Childhood Hematologic Malignancies in Ain Shams University Hospital: A Ten-Year Retrospective Study

Thesis

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Mahmoud Mohamed Shawiesh

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List of Abbreviations

ABVD	Adriamycin, bleomycin, vinblastine, dacarbazine
AIEOP	Associazione Italiana Ematologia Oncologia Pediatrica
ALL	Acute lymphoblastic leukemia
AML	Acute myeloid leukemia
ASCT	Autologous stem cell transplantation
BFM-SG	Berlin-Frankfurt-Munster-Study-Group
CBC	Complete blood picture
CMT	Combined modality therapy
CNS	Central nervous system
CR	Complete response
DFS	Disease-free survival
EFS	Event free survival
ESR	Erythrocyte sedimentation rate
FAB	French-American-British
FDG-PET	18F-fluorodeoxyglucose positron emission tomography
GPOH	German Pediatric Oncology and Hematology Group
HSCT	Hematopoietic stem cell transplantation
IPT	Immunophenotyping
MRC	Medical Research Council
MRD	Minimal residual disease
NK	Natural killer
OS	Overall survival
PD	Progressive disease
WHO	World Health Organization

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Abstract

Background: Hematopoietic neoplasms constitute more than 40% of malignancies in children and represent a wide range of disorders that include acut leukemias and lymphomas. **Aim:** We aimed to evaluate outcome of children with hematologic malignancies in Ain Shams University at Pediatric Oncology clinic with the use of the currant treatment protocols and assess the need for a more risk based adapted therapy. **Methods:** 194 patients with ALL, 42 with AML, 65 with NHL, and 29 HL patients, registered at Pediatric Oncology Clinic, Ain Shams University Children's Hospital from January 2005 through December 2014, were included in the study. ALL patients were treated according to a modified CCG 1991 and 1961 for standard and high risk respectively. Patients were stratified into 3 risk groups. SR, HR-SA and HR-AA. AML patients were treated according to a modified MRC based protocol, they included 3 risk groups, favorable, intermediate and high. NHL was classified into lymphoblastic lymphoma, mature B-NHL and anaplastic large cell lymphoma, and treated according to BFM protocols for the different entities. HL patients were stratified into 3 risk groups; low, intermediate and high, and were treated according to the ABVD regimen and. **Results:** For ALL patients, the mean age at diagnosis was 6.1±3.9 years, male: female ratio 1.3:1. The 10-year OS was 85.3% while the 10-year EFS was 80.4%. Pre-B patients had significantly better outcome than T-cell patients (OS 88.8% and 68.6%, P=0.001; EFS 83.2% and 66.7%, P=0.015 for pre-B and T-cell respectively). There was no significant difference regarding OS and EFS in patients receiving single versus double delayed intensification, however DDI had higher OS and EFS in SR and not in HR groups. In the AML group, EFS was 74.4% for the total group. 10-year OS for favorable and intermediate risk group were 83.3% and 60% respectively. For NHL group, OS and EFS of the total group

of NHL patients were 89.1% and 84.6% respectively. The 10-year OS and EFS of for HL patients were 88.9% and 75.9% being 100% for low and intermediate risk patients and 80% for high risk patients. **Conclusion:** Standard risk acute lymphoblastic leukemia treated with CCG 1991 had the highest relapse rate among other risk groups and international outcomes. The use of double delayed intensification showed no survival benefits. T-cell ALL still have inferior outcome as compared to Pre-B patients. The outcome in non-APL AML patients was relatively good yet it should be interpreted cautiously due to the small number of studied patients and the defect in our records and filing system. The use of 2-3 gm/m2 of methotrexate in B-NHL therapy showed a favorable outcome. Survival of Hodgkin lymphoma patients was lower than international rates and mandates the application of response based therapy.

INTRODUCTION

Cancer is the second commonest cause of death in children in the developed countries. Owing to highly specific diagnostic procedures and the introduction and continuous improvement of multimodal treatment strategies, the past decades have seen a marked rise in the probability of cure ***(Kaatsch 2010).***

Hematologic malignancies account for 9.5% of new cancer diagnoses in the United States. For the years 1975-2012, the NCI SEER program reports an incidence of 49.1 and 24.9 per 1000, 000 for leukemia and lymphoma respectively in children younger than 19 years of age ***(Howlader et al., 2015)***.

Acute leukemias account for about 40% of childhood cancers; of which acute lymphoblastic leukemia (ALL) comprises about 70-80% and acute myeloid leukemia (AML) about 10-15%. Presently, the cure rates in ALL in developed countries are as high as 79-86% using intensive protocols ***(Pui et al. 2010)***.

The incidence of childhood AML has been estimated to be between about 5 to 7 cases per million people per year. There is evidence for variation in the incidence among some racial and ethnic groups. For example, black children have an

incidence of 5.8 cases per million compared to 4.8 cases per million in Caucasian children. Children of Hispanic background have the highest incidence. Current therapy for AML involves the stabilization of the patient at the time of diagnosis followed by remission induction therapy and postremission intensification with chemotherapy or HSCT along with CNS prophylaxis ***(Golub and Arceci, 2006)***.

Lymphomas are the third most common group of cancers in children and adolescents after leukemias and brain tumors, accounting for 10-15% of newly diagnosed cancers. Hodgkin lymphoma comprises 40% of all childhood lymphomas. It occurs in 5-7 per 100, 000 population. The incidence is highest in late childhood and early adulthood (15-35 years). It is very uncommon under 5 years of age ***(Schwartz 2003)***.

Although Hodgkin lymphoma is considered a highly curative neoplasm, about one-third of all patients fail to respond to conventional chemotherapy alone or combined with radiotherapy, However, the outcome of patients with primary progressive disease (PD) defined as progression during induction treatment or within 90 days after the end of treatment is dismal. Treatment results with second-line chemotherapy produces low remission rates, with long-term disease-free survival (DFS) in 0% to 10% of patients with

primary progressive HD. Salvage radiotherapy is an effective treatment for localized relapsed HD ***(Engert et al. 2003).***

Non-Hodgkin lymphoma accounts for approximately 7% of cancers in children less than 20 years of age. It occurs most commonly in the second decade of life, and occurs less frequently in children younger than 3 years of age. With current treatments, about 80% of children and adolescents with NHL will survive at least 5 years ***(Gore & Trippett 2010)***.