Risk stratification of early cardiotoxicity In Children receiving chemotherapy in Pediatric oncology

Thesis submitted for the parial fulfillment of the master degree by

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2010

Abstract

This is a retrospective study of the record of 80 cancer patients at pediatric age group who presented to Children Cancer Hospital Egypt in the period from July 2007 to March 2009.All patients had various types of malignancy and received various chemotherapy protocols .This study included risk factors of cardiotoxicity which are age, sex, cumulative dose of anthracyclines, type of malignancy, mediastinal irradiation, concomitant chemotherapy and underlying cardiac lesions.

Keywords:

Cardiotoxicity, Pediatric oncology, Risk stratification, Chemotherapy,

Anthracyclines.

بسم الله الرحمن الرحيم

(قالوا سبحانك لا علم لنا إلا ما علمتنا

إنك أنت العليم الحكيم)

صدق الله العظيم

سورة البقرة

آية رقم(٣٢)

Dedication

With all my Love,

To my Father

(God bless his soul)

And Sweet Lovely Mother

ACKNOWLEDGMENT

I *wish to express my sincere gratitude to* **Prof. Dr. Zeinab Salah Selim** *Professor of Pediatrics. Faculty of Medicine, Cairo University not only for her outstanding support, generous advice, and valuable guidance, but without her support, this work wouldn't come to light.*

I *would like to express my sincere appreciation to* **Prof. Dr. Mohammad Ali Hegazi** *Professor of Pediatrics, Faculty of medicine, Cairo University for his help and constructive advice.*

I *am also deeply indebted to* **Dr. Wael Zekry Khaled**. *Lecturer of pediatric oncology, National Cancer Institute, Cairo University for his most valuable help and advice and meticulous supervision of this work.*

Mai Saeed El-Setouhi

List of contents

List of tables

List of figures

List of Abbreviations

2 D……..……..……..Tow dimensional
5-FU……...……..…….5-fluorouracil
ACE…….....…Angiotensin converting enzyme
ACEIs…….……..…. Angiotensin converting enzyme inhibitors
AIDS…..…….... Acquired immunodeficiency syndrome
ALL……..……..…..Acute Lymphoblastic leukemia
AML……..……..……...Acute Myeloid Leukemia
ANOVA…… Analysis of variance
ANP…..……..……...….... Atrial natriuretic peptide
ANT…..……..……..…Anthracyclines
AR……...……..…….....Aortic regurge
ARB……..……..……..Angiotensin receptor blockers
AS……..……..……...…..Aortic stenosis
ASD……...……..…..…Atrial Septal Defect
AV……..…….……Atrioventricular
AVSD……...……. Atrioventricular septal defect
BBB……...…….Bundle Branch Block
BNP…...……...….. B-natriuretic peptide
CAD……..…….……. coronary artery disease
CCHE……...……...……. Children Cancer Hospital Egypt
CCSG……...……..…… Children's Cancer Study Group
CHD……..……...……Congenital Heart Disease
CHF……...……..…Congestive heart Failure
CoQ10..……..……...Coenzyme Q10
CTC……...……..… Common toxicity Criteria
DAU…..…….……...……..... Daunomycin
DCM…...……...…….Dilated cardiomyopathy
Dd…..…..……..….. end-diastolic dimension

DOX…….…….....Doxorubicin
Ds…….…….…….. end-systolic dimension
DVT……..……..…….….Deep venous thrombosis
DZX…… Dexrazoxane
ECG…….…Electrocardiogram
ECOG…….. Eastern Cooperative Oncology Group
EF……..…...Ejection Fraction
EFS…….....Event Free Survival
ES…….....Ewing's Sarcoma
FS…….....Fraction Shortening
Gy……..Gray
HD……..……..……...Hodgkin's disease
HF……...…….Heart Failure
Hz……..Hertz
IGF-1……Insulin growth factor-1
IL-2…….. Interleukin-2
IMRD……...……... Intensity modulated radiotherapy
IV…….……Intravenous
K……Potassium
LR……..Low Risk
LV…….....Left ventricle
LVD……...……...Left ventricular dilatation
LVEF…….……..Left ventricular Ejection Fraction
LVFS……..….Left ventricular Fraction Shortening
Mg……..…Magnesium
MHZ……..……Mega Hertz.
MI…….……..myocardial infarction
M-Mode…….…Motion- Mode
MR……..Mitral regurge
NB…….....Neuroblastoma
NCI……...… National Cancer Institute

NHL…….....Non-Hodgkin Lymphoma
NS…….Not Significant
NYHA……...…. New York Heart Association
OS……...Osteosarcoma
PBF……...….Pressure blood flow
PDA……..……..…Patent Ductus Arteriosus
PET……... Positron-emission tomography
PS……...Pulmonary stenosis
PW…….....Pulsed wave
RAS……Reticular activating system
RHD……...……Rheumatic heart disease
RNA…….……..Radionuclide angiocardiography
ROS……...… Reactive oxygen species
RT……..Radiotherapy
SD……...….Standard deviation
SF……...Shortening Fraction
SR…….....Standard Risk
STEP…...System for Thalidomide Education and Prescribing Safety
SVT……..……..Supraventricular Tachycardia
SWT…..……..…Septal wall thickening
TGA…….....transposition of great arteries
UK…….….United Kingdom
US……...…….United States
VSD……...…….Ventricular septal defect
WT…….Wilm’s Tumor

Introduction

Cytostatic antibiotics of the anthracycline class are the best known of the chemotherapeutic agents that cause cardiotoxicity. Alkylating agents such as cyclophosphamide, ifosfamide, cisplatin, Bleomycin and mitoxantrone have also been associated with cardiotoxicity. Other agents that may induce a cardiac event include paclitaxel, etoposide, teniposide, the vinca alkaloids, fluorouracil, cytarabine, amsacrine, cladribine, asparaginase and tretinoin. Cardiotoxicity is rare with some agents, but may occur in >20% of patients treated with doxorubicin and daunorubicin , ***(Pai, et al., 2000).***

Cytotoxic drugs cause damage to cardiac cells, especially in combination with radiotherapy. Furthermore, cardiotoxicity increases with the cumulative dose and may lead to congestive heart failure and cardiomyopathy. Other factors, including age, gender, pre-existing cardiac disease, length of follow-up, route of administration, concomitant exposure to some chemotherapeutic drugs, trisomy 21 and black race, play a role in increasing the risk of cardiac dysfunction**. (** ***Nadia et al., 2008).***

The fact that anthracyclines are cardiotoxic seriously narrows their therapeutic index in cancer therapy. *The prevention of anthracycline-induced cardiotoxicity is particularly important in children who can be expected to survive for decades after being cured of their malignancy*. Attempts to reduce anthracycline cardiotoxicity have been directed towards: (i) decreasing myocardial concentrations of anthracyclines and their metabolites by dose limitation and schedule modification; (ii) developing less cardio-

toxic analogs; and (iii) concurrently administering cardioprotective agents to attenuate the effects of anthracyclines on the heart. As regards schedule modification, avoidance of anthracycline peak levels may reduce the pathologic and clinical cardiotoxicity, although this has not always been observed, (***Arussi et al., 2005).***

Cardiotoxicity may occur during or shortly after treatment, within days or weeks after treatment, or may not be apparent until months, and sometimes years, after completion of chemotherapy. Some diseases require aggressive treatment with chemotherapy including some cardiotoxic drugs such as: anthracyclines , 5-fluorouracil, cyclophosphamide and the taxoids, plus radiotherapy (Mediastinal Radiation).In addition some diseases require aggressive/ short period condensed courses like Acute Myeloid Leukemia, Burkitt's Lymphoma which ends in cardiotoxicity. (***Arussi et al., 2005).***

Patterns of cardiotoxicity:

Cardiac affection might be seen as an initial presentation in newly diagnosed cases of pediatric cancer. Such toxicity manifested by heterogeneous group of disorders, ranging from relatively benign arrhythmias to potentially lethal conditions such as myocardial ischemia/infarction and cardiomyopathy, Pericardial effusion, cardiomegaly or can be seen *very early* during the course of treatment like latent cardiac dysfunction, valvular lesions *(mitral or aortic regurge due to mediastinal radiation)*, and carotid intimal thickening. . Common cardiovascular manifestations of these therapies include heart failure, hypotension, hypertension, QT prolongation, arrhythmias, and thromboembolism, (***Edward, 2006).***