Serum Epidermal Growth Factor Receptor Level In Children With Brain Tumors

Thesis submitted in partial fulfillment for master degree in

Pediatrics

by

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بسم الله الرحمن الرحيم

قالوا سبحانك لا علم لنا إلا ما

علمتنا إنك أنت العليم

الحكيم

صدق الله العظيم

سورة البقرة الآية (٣٢)

Dedication

To:

Soul of my parents

To:

My Brother and sisters

To:

My sincere wife

To:

My lovely children

Raghad, Mohamed and Ahmed

Acknowledgment

First of all, I thank *Allah* to whom I relate any success in my life.

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Contents

List of Abbreviations

ADCC	Antibody-dependent cellular cytotoxicity
AFP	Alpha-fetoprotein
ALL	Acute Lymphoblastic Leukaemia
ATP	Adenosine triphosphate
CBT	Childhood Brain Tumors
CCG	Children's Cancer Study Group
cGy	centi-Gray
CNS	Central nervous system
CR 1	Cysteine-Rich 1
CRT	Cranial radiation therapy
CSF	Cerebro-spinal fluid
CT	Computed tomography
Cys	Cysteine
3D-CRT	Three-Dimensional Conformal Radiotherapy
DNA	Deoxyribo Nucleic Acid
EGF	Epidermal growth factor
EGFR	Epidermal Growth Factor Receptor
EGFR vIII	Epidermal Growth Factor Receptor variant three
ELISA	Enzyme linked immuno-sorbant assay
ErbB	Epidermal receptor binding-B
ERK	Epidermal receptor kinase
FDG	F-deoxyglucose
Fmol/ml	Femto mole per milliliter
GFR	Glomerular filteration rate
GH	Growth hormone
GnRH	Gonadotropin releasing hormone
HB-EGF	Heparin-binding epidermal growth factor-like growth factor
hCG	Human chorionic gondadotropin
Her-2	Human epidermal growth factor receptor-2
ICP	Intracranial pressure
ICT	Intracranial tension
IgG	Immunoglobulin G

INR	International normalized ratio
I Q	Intelligence quotient
KDa	Kilo-dalton
LEU	Leucine
MAbs	Monoclonal antibodies
MAPK	Mitogen activated protein kinase
MRA	Magnetic resonance angiography
MRI	Magnetic resonance imaging
mRNA	Messenger Ribo Nucleic Acid
N	Number
NF-1	Neurofibromatosis type 1
NOC	N-nitroso compounds
NS	No significance
NSCLC	Non-small cell lung cancer
NSS	Neurological severity scale
OSR	Overall survival rate
PET	Positron emission tomography
PI3K	Phosphatidyl inositol-3 kinase
PKC	Protein kinase c
PNET	Primitive neuroectodermal tumor
PNET-MB	Primitive neuroectodermal tumor-Medulloblastoma
P value	Probability value
RAS	Receptor activation signal
ROCs	Receiver operating characteristics curve
RTK	Receptor tyrosine kinase
SD	Standard deviation
Sig	Significance
Src	Signaling receptor-C
TGF-α	Transforming growth factor-α
TK ***TMB***	Tyrosine kinase Tetra-methyl benzidine
WHO	World Heath Organization

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Introduction

Brain tumors are a heterogeneous group of diseases that collectively are the second most frequent malignancy in childhood and adolescence. Mortality among this group approaches 45%. In addition, these patients have the highest morbidity, primarily neurologic, of all childhood malignancies. However, outcomes have improved over time with innovations in neurosurgery and radiation therapy as well as identification of chemotherapy as a therapeutic modality ***(Kuttesch et al., 2008).***

Epidermal Growth Factor Receptor (EGFR) is a transmembrane cell surface receptor that plays an important and complex role in a wide variety of pathophysiological disorders including cancer. EGFR is a member of tyrosine kinases. The ligand-binding component of EGFR resides on the exterior surface of the cell and can be activated by hormones, growth factors, neurotransmitters and other cellular regulators ***(Mendelson and Baselga, 2000).***

When EGFR is activated by epidermal growth factor and other ligands, a variety of complex intracellular signaling pathways are triggered resulting in regulation of diverse cellular processes such as cell division, cell survival and cell motility ***(Yarden and Sliwkowsky, 2001).***

Normally, EGFR activation is regulated. But when such regulation is disrupted, ongoing stimulation of cell replication results. This deregulation predisposes to the development and maintenance of cancer by initiating a continued uncontrolled cell proliferation. Deregulation may result from EGFR gene amplification that results in more growth factor receptors on the cell surface, increased EGFR transcription or translation that results in overexpression of cell surface growth factor receptors and increased EGFR- mediated signaling ***(Brugge and McCormick, 1999).***

Based on structure and function of EGFR, two antireceptor therapeutic strategies have been developed. The first strategy uses humanized monoclonal antibodies that block ligand binding to the extracellular domain. The second approach uses small-molecule inhibitors to inhibit the EGFR tyrosine kinase, which is on the cytoplasmic side of the receptor. A number of EGFR inhibitors have been developed that can arrest tumor growth and, in some cases, cause tumor regression. When used in combination with cytotoxic treatments, chemotherapy or radiation, EGFR inhibitors have been able to potentiate their anticancer activity ***(Ritter and Arteaga, 2003).***

Aim of the Work

The aim of this study is to assess serum epidermal growth factor receptor levels in children with brain tumors and to relate its level to different clinicopathological features of the patients

Brain Tumors

Tumors in childhood represent the second most common cause of death after accidents and malignant brain tumors are the first cause of cancer death among children. These tumors account for about 16% of all childhood malignancy being second only to leukemia ***(Baldwin and Preston-Martin, 2004).***

Incidence:

The incidence of childhood CNS tumors appeared to be on the rise. This higher incidence was likely due to the increased use of magnetic resonance imaging (MRI) to evaluate children with neurologic conditions and to an increase in microscopical confirmation techniques rather than true increase in the disease frequency **(*Pizzo et al., 2006).***

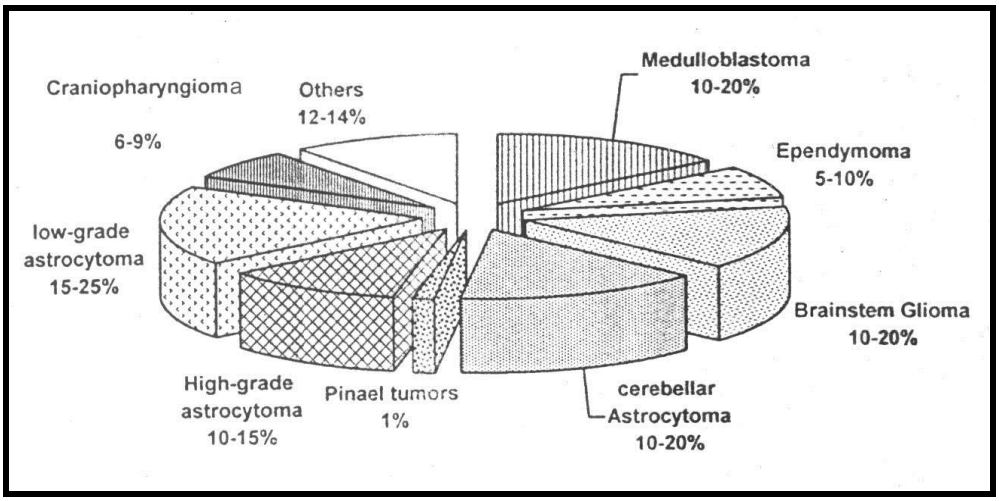

Fig. (1): Incidence of the common pediatric CNS tumors *(Pizzo et al., 2006).*