Retrospective Analysis of Clinical Epidemiology in Gastrointestinal Stromal Tumour

Thesis

Submitted for Partial Fulfillment of Master Degree in Clinical Oncology

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2018


وَمَنْ أَحْيَاهَا فَكَأَنَّمَا أَحْيَا النَّاسَ جَمِيعًا
And whoever saves one - it is as if he had saved mankind entirely.
سورة المائدة - آية 32
Holy Quran - 5:32

Acknowledgment

First and foremost, I feel always indebted to **ALLAH**, *the Most Kind and Most Merciful.*

I'd like to express my respectful thanks and profound gratitude to **Prof. Amr Lotfy Farag,** *Professor of Oncology and Nuclear Medicine, Faculty of Medicine- Ain Shams University for his keen guidance, kind supervision, valuable advice and continuous encouragement, which made possible the completion of this work.*

I am also delighted to express my deepest gratitude and thanks to **Dr/ Mai Mohammed Ali,** *Assistant Professor of Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for her kind care, continuous supervision, valuable instructions, constant help and great assistance throughout this work.*

I am deeply thankful to **Dr. Nesreen Ahmed Mosalam,** *Assistant Professor of Oncology and Nuclear Medicine, Faculty of Medicine, Ain Shams University, for her great help, active participation and guidance.*

I would like to express my hearty thanks to all **my family** *for their support till this work was completed.*

Last but not least my sincere thanks and appreciation to all my colleagues who helped me in this study.

Mustafa A. Azim

List of Contents

List of Tables

List of Tables (Cont...)

List of Figures

List of Figures cont...

List of Figures cont...

List of Abbreviations

Abb.	Full term
3D	*3 Dimensions*
AFIP	*Armed Force Institute of Pathology*
ASUH	*Ain Shams University Hospitals*
CD117	*Cluster of Differentiation 117*
CrCL	*Creatinin Clearance*
CT	*Computerized Tomography*
CTV	*Clinical Target Volume*
DDI	*Drug-Drug Interaction*
DNA	*Deoxyribonucleic Acid*
DOG-1	*Discovered on GIST-1*
ECG	*Electrocardiography*
ECOG	*Eastern Cooperative Oncology Group*
EORTC	*European Organization for Research and Treatment of Cancer*
ESMO	*European Sarcoma Network Working Group*
EUS	*Endoscopic Ultrasound*
FDA	*Food and Drug Administration*
GISTs	*Gastrointestinal Stromal Tumors*
HPF	*High Power Microscope Fields*
HTN	*Hypertension*
HU	*Hounsfield Unit*
ICC	*Interstitial Cells of Cajal*
IHC	*Immunohistochemistry*
IMRT	*Intensity Modulated Radiotherapy*
IQR	*Interquartile range*
MDT	*Multi Disciplinary Team*
MRI	*Magnetic Resonance Imaging*
NCCN	*National Comprehensive Cancer Network*
NCI	*National Cancer Institute*

List of Abbreviations (Cont...)

Abb.	Full term
OS	*Overall Survival*
PCR	*Polymerase Chain Reaction*
PET	*Positron Emission Tomography*
PFS	*Progression Free Survival*
PPI	*Proton Pump Inhibitors*
PTV	*Planning Target Volume*
R	*Linear Correlation Coefficient*
RECIST	*Response Evaluation Criteria in Solid Tumors*
SDH	*Succinate Dehydrogenase*
TKI	*Tyrosine Kinase Inhibitor*
US	*United States*
VEGFRs	*Vascular Endothelial Growth Factor Receptors*

ABSTRACT

Background: GIST is classified into mutation in either KIT or cluster of differentiation 117 (CD117) oncogene (85%), Platelet – drived growth factor receptor alpha gene (PDGFRA) (10%) or rarely B-Raf gene. C.Kit - which is mutated & activated in 80% of GIST- is an oncogene which encodes cell surface receptor Tyrosine Kinase TK (CD117) which is responsible for activation of multiple signaling cascades leading to cellular proliferation.

Aim of the Work: to explore the best management options of care for patients at Ain Shams University Hospitals (ASUH) by retrospectively analyzing epidemiological factors in Gastrointestinal stromal tumor patients and correlate them to clinical outcome; these factors are either patient or disease ones, while outcome include clinical benefits, survival and encountered toxicities.

Patients and Methods: this is a retrospective study. This study included 34 patients with GIST treated at the department of Clinical Oncology and Nuclear medicine, Ain Shams University between 2011 -2017 and followed up till 1-2017.

Results: many prognostic factors were selected for analysis to evaluate their impact on overall survival. Age, gender, site and size of tumor, mitotic index, histopathology, presence of metastasis at time of presentation and anemia all had no statistically significant impact on overall survival.

Conclusion: the prognosis of GIST is undoubtedly better than other sarcomas. No clear risk factor of GIST. Patient selection is paramount as to minimize the high cost of treatment. Tumor density must be known by Hounsfield unit before treatment to detect pseudo progression. Molecular analysis by PCR is very important to know sensitivity to treatment as a predictive biomarker. Patients should be kept on follow up for early detection of recurrence.

Keywords: *Epidemiology - Gastrointestinal Stromal Tumour - cluster of differentiation 117*

Introduction

Gastrointestinal Stromal tumors (GISTs) are the most common mesenchymal neoplasms of the gastrointestinal tract (GIT) i.e. sarcoma. The term GIST was first introduced by ***Mazur and Clark in 1983*** to describe non-epithelial tumors of the GI tract originating from pacemaker of smooth muscles (Interstitial Cells of Cajal (ICC)), stomach being the most common site (60%) with the best prognosis ***(Demetri, 2011)***.

GIST is classified into mutation in KIT also known as cluster of differentiation 117 (CD117) oncogene (85%), Platelet – drived growth factor receptor alpha gene (PDGFRA) (10%) or rarely B-Raf gene ***(Miettinen and Lasota, 2006).*** C.Kit - which is mutated & activated in 80% of GIST- is an oncogene which encodes cell surface receptor Tyrosine Kinase TK (CD117) which is responsible for activation of multiple signaling cascades leading to cellular proliferation ***(Harding and Tap, 2014).***

The epidemiologic data being collected are not precise and the proportion between benign and malignant is not clear e.g. 5000 new cases per year in United States, 30 new cases per-million per year in Sweden. On the data base of the European Organization for Research and Treatment of Cancer (EORTC) study collected from 14 countries the incidence was 4-5 cases per million per year, 20-30% of which were inoperable and metastatic ***(Cichoz-lach et al., 2008)***

In Egypt GIST represents 2.5% of gastrointestinal tumors. The majority of cases are at the age of 50-70 years being rare before the age of 40 years and the incidence is almost similar among men & women ***(Mokhtar et al., 2007).***

Anatomic sites of GIST are stomach 60%, small intestine 30%, rare sites are large intestine, œsophages and mesentry. Clinical presentation is not charactaristic e.g. abdominal pain,melena early satiety and weight loss. It may be asymptomatic and discovered incidentally during endoscopy, radiologic diagnostics or surgical intervention ***(Harding and Tap, 2014).***

Diagnosis is made with endoscopic guided biopsy or after surgical resection, investigated by a pathologist under the microscope identifying spindle cell (75%) or epithelioid cell (25%) to suspect GIST and then confirmed by immunohistochemistry (IHC). C.KIT (CD117) is being positive in 90% and Vimentin being positive in mesenchymal cells. In case C.KIT is negative, recently a newer antibody DOG1 (Discovered on GIST) can be used in suspicious tumors ***(Caram and Chugh, 2013).***

Radiologic imaging e.g. computerized tomography (CT) or magnetic resonance imaging (MRI) with contrast is used to locate site of lesion, evaluate signs of invasion and detect metastasis e.g. liver. In CT images large GISTs appear as heterogenous masses due to areas of tumor cells, bleeding and necrosis. In small GISTs, images show smooth, well defined intramural masses with homogeneous attenuation ***(Hersh et al., 2005).***

Prognosis depends on size and location of tumor and mitotic rate per 50 high power microscope fields (HPF). Size of at least 5cm is associated with good prognosis, while size more than 10cm is associated with high recurrence rate. Mitotic rate less than 5 per 50 HPF is associated with good prognosis while mitotic rate more than 5 is associated with high recurrence rate ***(Cichoz-lach et al, 2008)***.

Surgical resection is the main line of treatment in resectable and locally advanced diseases with 5 years survival rate up to 60% ***(Hrycek et al., 2005).*** Complete resection with negative margins is the goal. Lymphadenectomy is not required due to rare metastasis to lymph nodes. Laparoscopic surgery has been shown to be effective ***(Nguyen et al., 2006).*** Chemotherapy is not effective ***(Kantarjian et al., 2011).***

Metastasis to liver is the most common, and can be treated by ablation (destructing tumour using extreme heat) or embolization (blocking the blood flow to cancer cells) ***(National Comprehensive Cancer Network (NCCN), 2017)***.

Imatimib (Glivec) is an oral tyrosine kinase inhibitor (TKI) which targets both C.KIT and PDGFRα proteins leading to decreasing the tumor cell growth. It can be used as an adjuvant therapy or neo-adjuvant to shrink the tumor preoperatively and in advanced GIST. The initial administration of this drug could lead to internal bleeding due to fragile blood vessels, so physicians must follow patients