التوجهات الحديثة في علاج سرطان الغدة الدرقية النخاعي

توطئة للحصول على درجة الماجستير فى علاج الاورام والطب النووى

مقدمة من

الطبيبة/رشا عبد الفتاح زين

بكالوريوس الطب والجراحة

كلية الطب – جامعة عين شمس

تحت اشراف

ا.د/ايمان محمد فؤاد

استاذ ورئيس قسم علاج الاورام والطب النووى

كلية الطب - جامعة عين شمس

ا.م.د/عمرو لطفى فرج

استاذ مساعد علاج الاورام والطب النووى

كلية الطب- جامعة عين شمس

أ.م.د/ناجى سامى جبران

استاذ مساعد علاج الاورام والطب النووى

كلية الطب- جامعة عين شمس

كلية الطب

جامعة عين شمس

2014

Novel Approaches in management of Medullary Thyroid Cancer

Essay

Submitted for partial fulfillment of master degree in clinical oncology and nuclear medicine

By

Rasha Abd ELfattah Zein

M.B.B.CH
Ain Shams University

Under supervision of

Prof. Dr./Iman Mohamed Fouad

Professor and Head of Clinical Oncology and Nuclear Medicine Department Ain Shams University

Prof. Dr. /Amr Lotfy Farag

Assistant Professor of Clinical Oncology and Nuclear Medicine Department Ain Shams University

Prof. Dr./Nagy Samy Gobran

Assistant Professor of Clinical Oncology and Nuclear Medicine Department Ain Shams University

Faculty of Medicine

Ain Shams University

2014

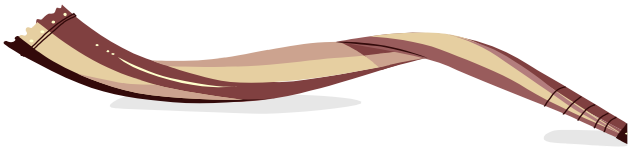
ACKNOWLEDGEMENT

First of all, Thanks to Allah

I would like to express my deepest thanks, gratitude and profound respect to my honored professor, ***Prof. Dr./Iman Mohamed Fouad*** *Professor and Head of Clinical Oncology and Nuclear Medicine Department Ain Shams University, for her meticulous supervision. I consider myself fortunate to work under her supervision. Her constant encouragement and constructive guidance were of great importance for the initiation, progress and completion of this work.*

I would like to extend my thanks to ***Prof. Dr. /AmrLotfyFarag*** *Assistant Professor of Clinical Oncology and Nuclear Medicine Department Ain Shams University , for his active participation in this work. he really did his best to get this work fulfilled.*

My special thanks to ***Prof. Dr./Nagy SamyGobran*** *Assistant Professor of Clinical Oncology and Nuclear Medicine Department Ain Shams University , who offered me a lot of guidance, continuous encouragement and advice while supervision every step in this work.*



RashaAbdELfattahZein

List of Contents

List of Abbreviation

MTC	Medullary thyroid carcinoma
MEN	multiple endocrine neoplasia
TSH	Thyroid-stimulating hormone
CEA	Carcinoembryonic antigen
CT	computed tomography
FNA	fine needle aspiration
^{99m}Tc(V)-DMSA	Technetium-99mPentavalentDimercaptosuccinic Acid
MIBG	RadioiodinatedMetaiodobenzylguanidine
SRS	Somatostatin Receptor Scintigraphy
^{201}Tl	^{201}Thalium
MIBI	^{99m}Tc-sestamibi
CCK	Cholecystokinin
PET	Positron Emission Tomography
^{18}F-FDG	^{18}F-fluorodeoxyglucose
^{18}FDOPA	^{18}F- fluoro-dihydroxy-fluorophenylalanine
PTEN	Phosphatase and tensin homolog
PI3K	Phosphatidylinositol-4,5-bisphosphate 3-kinase
mTOR	Mammalian target of rapamycin
ATA Guidelines	American Thyroid AssociationGuidelines
ETA Guidelines	European Thyroid AssociationGuidelines
IRRC	Investor Responsibility Research Center
TRH	Thyroid releasing hormone

List of Tables

List of Figures

Dedication

Dedicated of :

Soul of my Mother

Soul of May Father

My husband

My sister and Brothers

Introduction

According to the National Cancer Institute, , The age-adjusted incidence rate of thyroid cancer around the world is 11.6 per 100,000 men and women per year. These rates are based on cases diagnosed in 2005-2009 from 18 SEER geographic area.(***NCI.SEER*Stat 6.1. 2005)***

In Egypt age standardized incidence of thyroid cancer rate is 2.0 per 100 000 men and women (1.2 men, 2.7women). Medullary type represents 2.8%of these cases. (***SEER*Stat 6.1. 2005)***

Medullary thyroid cancer (MTC) is a form of thyroid carcinomawhich originates from the parafollicular cells (C cells), which produce the hormone calcitonin. (***Hu ,et al., 2008***)

Medullary tumors are the third most common of all thyroid cancers. They make up about 3% of all thyroid cancer cases.Approximately 25% of medullary thyroid cancer is genetic in nature, caused by a mutation in the RET proto-oncogene. This form is classified as familial MTC. When MTC occurs by itself it is termed sporadic MTC. When it coexists with tumors of the parathyroid gland, medullary component of the adrenal glands (pheochromocytoma) it is called multiple endocrine neoplasia type 2 (MEN2).(***Dionigi, et al., 2007***).

The cause of medullary carcinoma of the thyroid (MTC) is unknown. Unlike other types of thyroid cancer, MTC 1is less likely to be caused by radiation therapy to the neck given to treat other cancers during childhood. (***NCCN Guidelines in Oncology,2014)***

Medullary thyroid carcinoma (MTC), a calcitonin-producing tumor that occurs in familial and sporadic forms, can be monitored satisfactorily with measurements of calcitonin and CEA in serum. However, locating the tumor site may be difficult. In the current review of the experience with four new radionuclide tracers for MTC, the relative value of each of these procedures is outlined. Total body imaging using TI-201 chloride and Tc-99m (V) DMSA are both sensitive techniques that can be used for the detection and follow-up of MTC. Imaging using I-131 MIBG and I-131 anti-CEA antibodies/fragments should be performed once the diagnosis and the tumor site have been established, to evaluate if patients might be amenable for therapy with one of these radiopharmaceuticals.(**Galloway *,et al.,1996)***

The primary treatment of clinically apparent hereditary or sporadic MTC is total thyroidectomy with dissection ofipsilateral and central neck compartments with the aim of removing all neoplastic tissue. Contralateral dissection is frequently, but not unanimously recommended.(***Schlumberger M, et al.,2003***)

Chemotherapy and radiation do not work very well for this type of cancer. Radiation is used in some patients after surgery. Post-operative conformal EBRT provides durable locoregional disease control for high-riskpatients if disease is reduced to microscopic burden. Patients with gross disease face significantly worse outcomes. IMRT may significantly reduce chronic radiation morbidity, but requires further study. (***UrbanoTG,et al., 2007***)

With the discovery of the *ret* proto-oncogene and its integral role in the pathogenesis of MTC, a new class of therapies has been developed, aimed at the molecular pathways central to the development and

progression of MTC. *RET* is part of the receptor tyrosine kinase family and has been shown to signal through multiple downstream pathways, including the extracellular signal–related kinase (ERK), phosphatidyl-inositol 3-kinase (PI3K)/Akt, p38 mitogen-activated protein kinase (MAPK), and c-Jun N-terminal kinase pathways .(***Ball DW,et al.,2007***)

Approximately 86% of those with medullary carcinoma of the thyroid live at least 5 years after diagnosis. The 10-year survival rate is 65% .Complications may include cancer spreads to other areas of the body and, parathyroid glands are accidentally removed during surgery. (***NCCN Guidelines in Oncology, 2010)***

Aim of the Work

Review the standard and novel ways for diagnosis and treatment of medullary thyroid cancer with reviewing the prognostic factors affecting the outcome.

(1)Incidence

Medullary thyroid carcinoma (MTC) is a malignant epithelial tumor of the thyroid gland that exhibits C-cell differentiation. C cells arise from the ultimobranchial body, which is derived from the fourth pharyngeal pouch, and they are found in the upper and middle areas of the thyroid lobes. These cells produce calcitonin, a hormone involved in calcium homeostasis. While a number (20%) of MTCs are associated with the autosomal-dominant inherited multiple endocrine neoplasia (MEN) syndromes (specifically MEN2A and MEN2B), most (80%) cases are sporadic. Germline or somatic mutations of the RET gene are characteristic of this tumor. They usually involve an activating point mutation of 10q11.2. Specifically, codon 634 in exon 11 is most common in MEN2A, while codon 918 in exon 16 is most common in MEN2B. MTC accounts for approximately 5 to 8% of all thyroid malignancies.***(Kloos RT, et al.,2009).***

According to the National Cancer Institute, , The age-adjusted incidence rate of thyroid cancer around the world is 11.6 per 100,000 men and women per year. These rates are based on cases diagnosed in 2005-2009 from 18 SEER geographic area.(***NCI.SEER*Stat 6.1. 2005).***

In Egypt age standardized incidence of thyroid cancer rate is 2.0 per 100 000 men and women (1.2 men, 2.7women). Medullary type represents 2.8%of these cases. (***SEER*Stat 6.1. 2005).***

The number of new cases of thyroid cancer in USA was 12.2 per 100,000 men and women per year. The number of deaths was 0.5 per 100,000 men and women per year. These rates are age-adjusted and based on 2006-2010 cases and deaths. There are an estimated 534,973 people currently living with thyroid cancer in the United States. Estimated new

cases in 2013 are60,220,which represent 3.6%. of all new cancer cases. Estimated deaths in 2013 are 1,850 which represent0.3% of all new cancerdeaths.(***NCI.SEER*Stat 6.1. 2013).***

Around the world incidence of thyroid cancer is 213,179(thousands) which represent 3.1% of all types of cancer .in Egypt incidence is 360(thousands) which represent 1.0% all types of cancer in Egypt.(***GLOBOCAN.,2008*).**

Risk factors

***Exposure to Radiation**

The cause of medullary carcinoma of the thyroid (MTC) is unknown. Unlike other types of thyroid cancer, MTC is less likely to be caused by radiation therapy to the neck given to treat other cancers during childhood **(*Ladenson P, et al.,2007*)**.

***Age**

Sporadic cases usually present in fifth or sixth decade .MTC affiliated with MEN 2B tends to be most aggressive, with the development of invasive cancer in patients as young as 1 year. FMTC is the least aggressive, with invasive cancer not presenting until 20 to 30 years of age. (***Ladenson P, et al.,2007).***

***Heredity/Genetics/Family History**

An estimated 20% of patients with medullary thyroid cancer (MTC) develop the condition due to an abnormal gene. This gene can be passed on to offspring. Thyroid cancer that develops due to this genetic abnormality is called familial medullary thyroid carcinoma (FMTC). Family members who share this gene abnormality are at a greatly increased risk of medullary thyroid cancer. **(*Ladenson P, et al.,2007*)**. The hereditary forms of MTC are MEN-2A, MEN-2B, and FMTC. All

these disorders are inherited in an autosomal dominant pattern, and have variable penetranceas shown in table (1).

Table (1): Percentages in table below refer to how large fraction of people with the MEN type develop the neoplasia type.

Feature	MEN 1	MEN 2		
		MEN 2A	MEN 2B	FMTC
Pancreatic tumors	gastrinoma (50%), insulinoma(20%), vipoma, glucagonoma, PPoma	-	-	-
Pituitary adenoma	66%	-	-	-
Angiofibroma	64%*	-	-	-
Lipoma	17%*	-	-	-
Parathyroid hyperplasia	90%	50%	-	-
Medullary thyroid carcinoma	-	100%	85%	100%
Pheochromocytoma	-	>33%	50%	-
Marfanoid body habitus	-	-	80%	-
Mucosal neuroma	-	-	100%	-
Gene(s)	MEN1	RET	RET	RET NTRK1
Approx. prevalence	1 in 35,000	1 in 40,000	1 in 1,000,000	
Initial description (year)	1954	1961	1965	

FMTC = familial medullary thyroid cancer

MEN 2B is sometimes known as MEN 3 and the designation varies by institution (***Moline J,et al.,.2011***)

The genetic mutation in familial MTC is in the *ret* proto-oncogene, which is mapped to chromosome 10q11.2. The *ret* gene encodes a transmembrane tyrosine kinase receptor. Because *ret* is a proto-oncogene, only a single point mutation is required for malignant transformation. The first germline mutation of the *ret* gene was identified in patients in 1993. The currently known mutations encode >95% of cases of hereditary MTC. The most common mutation in MEN-2A is in codon 634, occurring in 80% of patients. The codon most frequently associated with MEN-2B is a codon 918 mutation. (***Machens A, et al.,2006***).

Approximately 20% of patients with MTC have a germline mutation in the *ret* proto-oncogene. Even patients with apparently sporadic disease have a 6%–10% chance of having a germline*ret* mutation. Therefore, all patients with a diagnosis of MTC should undergo genetic testing. (***MachensA,et al.,2006***).

The significance of a genetic mutation for a patient and their family cannot be underestimated. It is important that, prior to screening for genetic mutations, patients receive appropriate genetic counseling. The risks and benefits of genetic testing should be carefully discussed with the patient and their family. Once a patient is found to be positive for a *ret* mutation, they must be carefully counseled regarding the risks to additional family members. At-risk family members need to be identified and should undergo genetic testing, because patients that are identified as *ret* mutation carriers can be offered a prophylactic thyroidectomy.***(Skinner MA,et al.,2005).***

Among *ret*mutations, there is significant variation in the aggressiveness of the MTC that develops. Currently, *ret* mutations are classified into three groups based on the level of risk (or aggressiveness)