Role of clinical pharmacogenetics & Histopathological to identification of Treated Thyroid Cancer

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ABSTRACT: Lately, an increased incidence of thyroid cancer has been reported around the world. In Libya there are a few studies which have investigated thyroid cancer, so we conduct this study by nanotechnology technique in clinical pharmacology through pharmacogenetics technical the best scientific way by in vivo or in-vitro identification how Xenobiotic-metabolizing enzymes are widely polymorphic and confer interindividual variation in the ability to detoxify carcinogens or to activate pro-carcinogens. A common polymorphism of cytochrome P450 2D6 (CYP2D6) results in lack of enzyme activity and has been associated with an altered susceptibility to several cancers

to explore the incidence and the clinical pathological presentations of thyroid cancer among patients diagnosed in Histopathology department at Tripoli Medical center. from 210 patients diagnosed with thyroid cancer during the period from January 2002 till December 2012 have been analyzed. There were 176 Female and 34 Male patients. The histopathological pattern of the disease was 61.43% papillary cancer, 13.33% follicular, 7.14 % medullary, 5.24% Hurtle cell carcinoma,4.29 % lymphoid tumor, 2.3% anaplastic, and the other histological types were 4.76%. We concluded that Thyroid cancer is more common in female compared to male. The most common histopathological pattern was for Papillary carcinoma (61.43%). We further need multicenter studiesof thyroid malignancy to investigate and to know the national pattern and **TREND OF THYROID CANCER IN.**

KEY WARDS THYROID CANCER., PAPILLARY THYROID CANCER, INCIDENCE.CYP 450

INTRODUCTION:

Thyroid cancer had marked variation in the prevalence all over the world[1–2] it is more common in female compared with male in the third, fourth, and fifth decade of life[3.I]in Iodine-rich areas higher frequency is papillary carcinoma of thyroid gland was noticed[4]. Reported incidence of both benign and malignant lesions in surgically treated thyroid swelling varies widely from one geographically area to other [5-6]and the principle disease of thyroid gland are goiter "diffuse or nodular ", hypothyroidism, hyperthyroidism and neoplasm[7].Pharmacogenetics is the study of inherited variations in the DNA sequence of known genes, e.g., involved in drug metabolic pathways, which can affect individual responses to drugs, both in terms of therapeutic responses and adverse effects[8]pharmacokinetics and pharmacodynamics of a drug, holds promise as a means to provide greater safety and efficacy in drug design and development[9],and there's some factors effected on cancer such as polymorphism there for we joined our study with clinical pharmacology and pharmacogenetics. In Libya the incidence of thyroid cancer is 0.9% of all cancer cases and the cure rate per 100.000 Population was 0.65 (Benghazi Cancer Registry 2004). In USA thyroid cancer account for less than 1% of all malignances (2% for women and 0.5% of men) and thyroid cancer was responsible for six deaths per million people annually [8].In south Africa the incidence of thyroid cancer was 5.4% and in Karachi Pakistan

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was 14.35% [4]. in Riyadh, Saudi Arabia the studies reported higher incidence of thyroid malignancy ranging from 21% to 29%[4,5,9].In Nigeria studies showed an overall incidence for thyroid malignancy of 11% and the commonest was follicular[10]. The complex metabolism of metamizole has been the subject of many in-vivo studies (Levy et al., 1995). In the pharmacokinetics of metamizole, the specific CYP catalyzing the formation of the primary metabolic step to the active metabolite 4-aminoantipyrine (4-AA) is still not known. The biotransformation pathway of metamizole (Levy, 1986) and [11] is well established. It is no enzymatically dealkylated in the gastric juice to the active moiety 4-methylaminoantipyrine (4-MAA)[12]. 4-MAA undergoes demethylation in the liver to 4- aminoantipyrine).AA undergoes further phase-II biotransformation to acetyl-aminoantipyrine (AAA) by the polymorphic N- acetyltransferase.

AIM OF THE STUDY :-

The aims of this study divided to tow purpose first purple was to describe the incidence and the clinic pathological of thyroid cancer among patients diagnosed in histopathology department and the second purple investigate which specific cytochrome P450 enzymes are involved in the biotransformation of the analgesic-antipyretic common uses with some anti-cancer therapeutics in Tripoli Medical Center and Georg-August University, Medical Center Gottingen clinical pharmacology department in ten years' period from January 2002 till December 2012 and to compare it with other studies.

The Methods :-

Retrospective study of 210 cases diagnosed of thyroid cancer in Histopathology department at Tripoli Medical Center over 10 years' period from January 2002 till December 2012. Demographic characteristics (age and gender, clinical information).Biotransformation was studied in the subcellular fraction termed microsomes, which is a fraction of membrane vesicles corresponding to the endoplasmic reticulum in the intact cell. Microsomes were isolated from rat and human liver tissues. The impact of genetic polymorphism in one of the enzymes apparently involved in biotransformation of the studied drugs, CYP2C19, was analyzed in the used human liver samples by allelic discrimination. The microsomes were incubated with the substrates Metamizole and Aminopyrine, respectively. The produced metabolites were identified and quantified using HPLC analysis. Enzyme kinetic data analysis was finally used to determine enzyme kinetic.

Results:-

Histological patterns of 210 of operated cases of thyroid cancer were studied. We fount out that 61.43% of the cases had Papillary cancer, 13.33% had Follicular, 7.14% had Medullary, 5.24% had Hurtle Cell Carcinoma, 4.29% had lymphoid tumor, 2.3% had anaplastic, and the other histological types were 4.76% as shown in Table (1).The mean age of patient was45 years (rang was 15 -84 years) and there were 176 females (83.8%) and 34 Male (16.2%), the female to male ratio was 4:1. The mean age for Anaplastic type was 64 years of age and 40 ,34,34,55 years for Papillary, Follicular, Medullary Hurtle cell tumors respectively as shown inTable (1).

Table (1) Theft histopathological types, and the mean age and gender ration for each type

Histopathology	No.	%	MEAN AGE	SEX F/M
Papillary	129	61.43	16-84	114/15
Follicular	28	13.33	25-84	25/3
Medullary	15	7.14	15-85	6/3
Hurtle cell carcinoma	11	5.24	45-84	6/2
Lymphoid	9	4.29	35-85	7/4
Anaplastic	8	3.81	45-84	10/5
Others	10	4.76	15-84	8/2
ALL	210	100	15-85	176/34

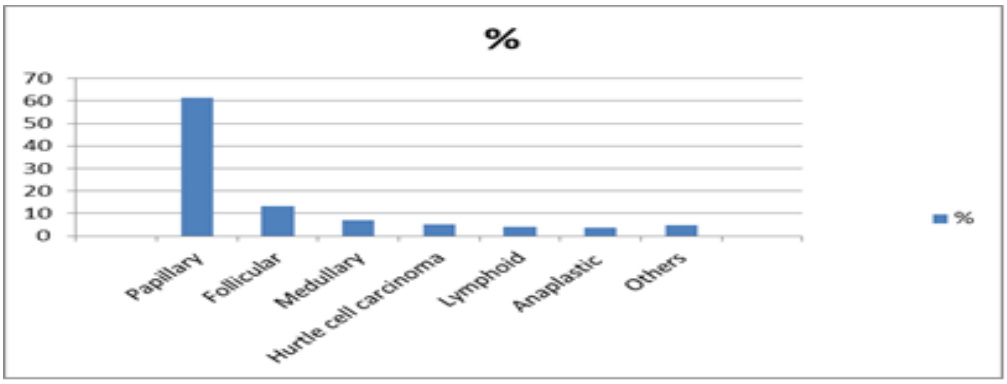

Fig.1histopathological types, and the mean age and gender ration for each type

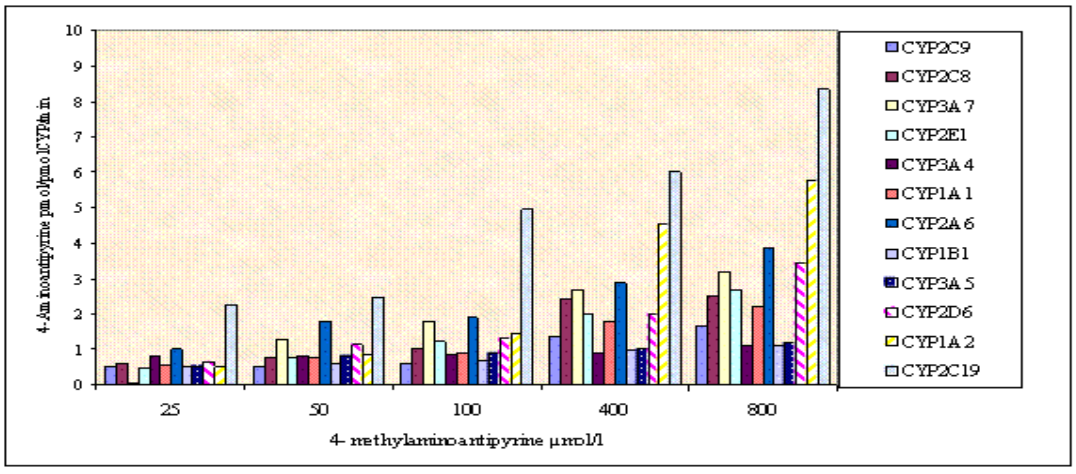

Fig.2 **Cytochrome P450 isozymes active in the in-vitro demethylation of 4-methylaminoantipyrine. 4- MAA was incubated with microsomes expressing human recombinant P450 isozymes (600 nMol/µl) for 20 min and the concentrations of 4-methylaminoantipyrine were 25, 50, 100, 400, 800 µmol/l. The formation of 4-aminantipyrine AA was monitored by HPLC analysis with UV detection. Results are given as means of duplicate incubations.**

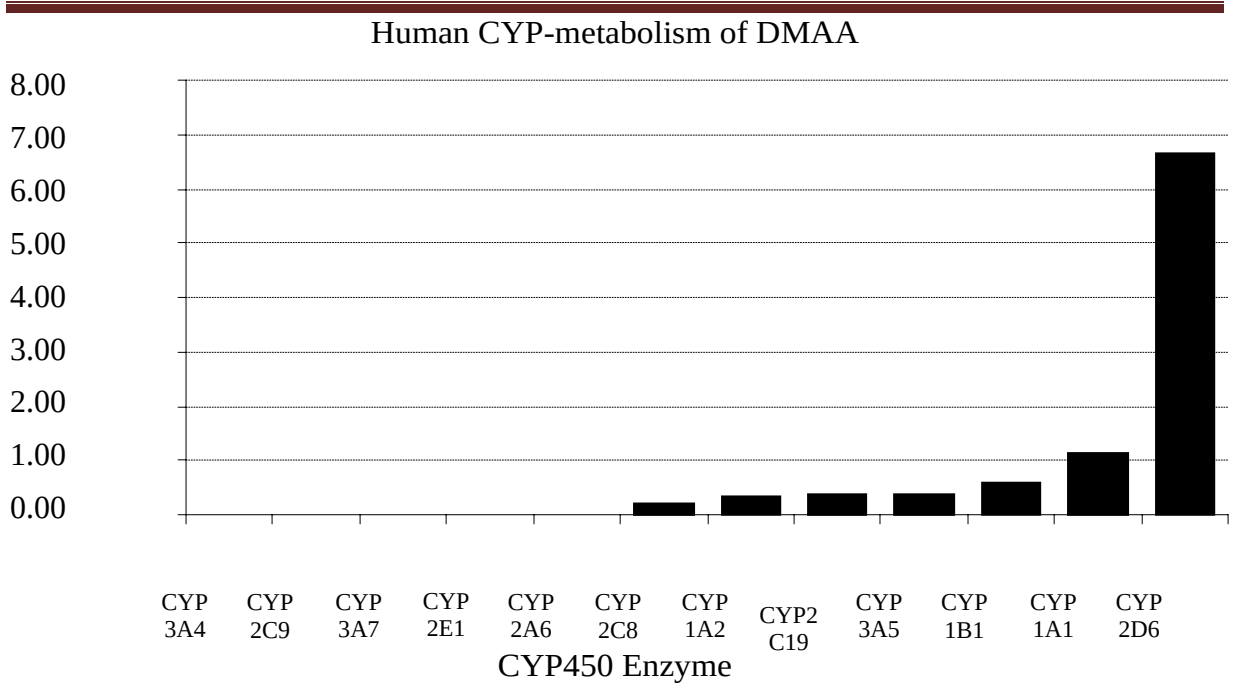

Fig. 3-Calculated intrinsic clearance of 4-dimethylaminoantipyrine by specific human cytochrome P450 enzymes after incubation of 4-DMAA with microsomes expressing human recombinant P450 isozymes (600 nmo/µl) for 20 min. The formation of 4-methylaminantipyrine (MAA) was monitored by HPLC analysis with UV detection. Results are given as means of duplicateincubations.

DISCUSSION:

Thyroid cancer is relatively rare neoplasm worldwide accounting for approximately 1-5 % of all cancer in female and less than 2% in male[11]. Although the incidence of thyroid cancer is relatively rare it is the most endocrine malignancy worldwide[11]. While the international incidence varies considerably, a fairly consistent female to male ratio of 3:1 is observed in almost all areas and ethnic groups[12].Thyroid cancer in Saudi Arabia were ranked as a second most common cancer among females and fourteenth among male with ratio of Female to male of 2:1[13]. The most common histopathological pattern in Saudi Arabia was for Papillary carcinoma which accounted for50% of the cases, followed by follicular carcinoma 4.3%, Lymphoma 1.1%, Lymphocytic thyroiditis with Papillary carcinoma 9.8 % and others types accounted for 34.7%[14]. Thyroid tumors usually present as a one side painless thyroid nodule in a clinically euothyroid patients.In Libya the histopathological types of Thyroid cancer were; Papillary carcinoma 46.6%, followed by Follicular carcinoma 45%, Medullary carcinoma 4.4 % and Anaplastic 5%[15]. According torecent studying Libya which has been conducted in 2003, the Papillary carcinoma type accounted for 65%, Follicular carcinoma for 24.5%, Medullary 6.3% and Anaplastic 2.1%[16]. Our present study compared with other studies in Libya found that 61.43% of the cases had Papillary carcinoma which was higher than the incidence of Papillary carcinoma in 1988, were it was 46.6% and almost near that incidence found by the study conducted in 2003, were it was 65%. For the Follicular carcinoma, the incidence of our study (13.3%) was lower than the study of 1988 which found that the incidence of Follicular cancer was 45% and that of 2003 which found that the incidence was 24.5%. For the Medullary carcinoma, the incidences found in our study and 1988 and the 2003 were comparable with 7.14%, 4.4% 6.3% in order., 5.24% had Hurtle Cell Carcinoma, 4.29 % had lymphoid tumor, 2.3 % had Anaplastic in comparison with 1988 were it was 5%and in2003 it was 2.1%, and other histological type was 4.76%. The study showed a relative higher incidence of Papillary carcinoma as well as Follicular carcinoma. In Nigeria

the Follicular type was the commonest type of Thyroid cancer and in Saudi Arabia papillary carcinoma form only 50% of the cases. This is consistent with the changing pattern of thyroid cancer[22]. In our study there was an increased incidence of thyroid cancer in female were we fined the ratio of female to male to be 4:1. In Saudi Arabia the ratio was 2:1 and the international figures was almost 3:1. Our finding was more consistent with the international incidence of thyroid cancer. In almost all areas and ethnic groups, the mean age of our group of patients was similar to that reported in other areas around the world.

The common use of fine needle aspiration technology in late 1980s, is the most cost effective and available method for identifying thyroid tumors[17] and with combination of thyroid ultrasound examination the diagnosis of smaller thyroid tumors have been facilitated[18]. Also the assessment of thyroid nodule to diagnose occult thyroid carcinoma had become feasible[19]. Large retrospective studies have suggested a tendency for improved outcomes over the past few years. This is thought to be a consequence of the increasing use of total thyroidectomy and I^{131} ablation, as well as other factors such as the use of serum thyroglobulin to monitor for recurrence and the more effective suppression of thyroid stimulating hormone levels in the blood[20-21]. microsomes expressing individual recombinant human CYP (CYP1A2, CYP1A1, CYP2C19, CYP2A6, CYP2D6, CYP3A4, CYP3A5, CYP3A7, CYP2C8, CYP2C9 and CYP2E1). Were incubated with different five concentrations from 4-methylaminoantipyrine.

CONCLUSION:

The study presented the clinic-pathological and pharmacogenetics patterns of thyroid cancer in 10 years' period from January 2002 till December 2012 at Tripoli Medical Center which works as the main Hospital in the west of Libya. Thyroid cancer is more common in females compared to males. The most common pattern for the thyroid cancer was for papillary carcinoma with an incidence of 61.43%. Finally, we need to have multicenter studiesfor thyroid malignancy to investigate the national pattern and trend of thyroid cancer and polymorphism's effected on the methods of treatment of thyroid cancer, poor metabolizer genotype is associated with a protective effect against PTC. This could be explained by a possible role of CYP2D6 on the metabolic activation of putative environmental chemical thyroid carcinogens or by linkage to another cancer-causing gene.

Altogether, these findings suggest that CYP2C19 and CYP2D6 are medically important enzymes responsible for the metabolism of therapeutic agents on the analgesic-antipyretic drugs, Metamizole and Aminopyrine and the role of the genetic polymorphisms in the genes coding for these enzymes for adverse effects should be further studied.

دور علم الوراثة الدوائية السريرية وعلم الأنسجة في تحديد سرطان الغدة الدرقية.

المستخلص: في الآونة الأخيرة، تم الإبلاغ عن زيادة الإصابة بسرطان الغدة الدرقية في جميع أنحاء العالم. وفي ليبيا ، هناك عدد قليل من الدراسات التي حققت في سرطان الغدة الدرقية ، لذلك نجري هذه الدراسة بتقنية النانو في علم العقاقير الإكلينيكي من خلال علم الوراثة الدوائية أفضل طريقة علمية عن طريق تحديد في الجسم الحي أو في المختبر كيف تكون إنزيمات الأيض للأجانب الحيوية متعددة الأشكال على نطاق واسع وتمنح الأفراد الاختلاف في القدرة على إزالة السموم من المواد المسرطنة أو تفعيل المواد المسببة للسرطان. يؤدي تعدد الأشكال الشائع للسيتوكروم P450 2D6 (CYP2D6) إلى نقص نشاط الإنزيم وقد ارتبط بقابلية متغيرة للإصابة بالعديد من السرطانات

لاستكشاف الإصابة والعروض السريرية المرضية لسرطان الغدة الدرقية بين المرضى الذين تم تشخيصهم في قسم التشريح المرضي في مركز طرابلس الطبي. من 210 مريض تم تشخيص إصابتهم بسرطان الغدة الدرقية خلال الفترة من يناير 2002 حتى ديسمبر 2012 تم تحليلها. كان هناك 176 من الإناث و 34 من الذكور. كان النمط النسجي المرضي للمرض 61.43٪ سرطان حليمي ، 13.33٪ جرابي ، 7.14٪ نخاع ، 5.24٪ سرطان خلايا سلحفاة ، 4.29٪ ورم ليمفاوي ، 2.3٪ كشمي ، والأنواع النسيجية الأخرى 4.76٪. خلصنا إلى أن سرطان الغدة الدرقية أكثر

شيوعًا عند الإناث مقارنة بالذكور. كان النمط النسيجي المرضي الأكثر شيوعًا هو السرطان الحليمي (61.43٪). نحن بحاجة أيضًا إلى دراسات متعددة المراكز حول ورم الغدة الدرقية الخبيث للتحقيق ومعرفة النمط والاتجاه الوطني لسرطان الغدة الدرقية.

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