iJRASET
International Journal For Research in Applied Science and Engineering Technology

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY

Volume: 7 **Issue:** III **Month of publication:** March 2019

DOI: http://doi.org/10.22214/ijraset.2019.3086

www.ijraset.com

Call: 08813907089 | E-mail ID: ijraset@gmail.com

International Journal for Research in Applied Science & Engineering Technology (IJRASET)
ISSN: 2321-9653; IC Value: 45.98; SJ Impact Factor: 6.887
Volume 7 Issue III, Mar 2019- Available at www.ijraset.com

Thyroid Function Tests Status among new Diagnosed and under Treatment Cases of Chronic Myeloid Leukemia

Alaa E. Hassan[1], Aula G. Hamid[2], Doha I. Abdulrahman[3], Waddaha M. Noah[4], Marwa A. Mohammed[5]. Tasneem H. Hussein[6], Tasneem A. Basher[7], Thurya S. Mortada[8]

[1, 2, 3]*Bahri University- Faculty of medicine*

[4] *Alneelain University- Faculty of medicine*

[5, 6, 7, 8]*Alzaeim Alazhary University-Faculty of medicine.*

Abstract: ***As chronic myeloid leukemia become a regular disease, spreading regardless, age, gender and race with highly incidences. Anti-proliferative drugs used in CML are mainly tyrosine kinase inhibitors, work as anti-proliferative agents. Side effects of these drugs needed to be checked. So this study aimed to evaluate thyroid function test among CML patients, from different location of Sudan. They were new case group, as no anti-proliferative drug was administered yet, beside group receiving anti-proliferative drug. Blood samples were collected from both groups and measured for TFTs via enzyme linked immunoassay (ELISA) kit and device. Data analyzed with statistical program SPSS. All CML patients were presented with increased levels of TFTs, T3, T4 and TSH. In regard of treatment administration, CML patients showed increased levels of TFT more than new cases, but both were increased than reference ranges giving significant differences as P value for each was less than 0.05.***

Keyword: thyroid function test, Enzyme linked immunoassay, anti-proliferative and statistical.

I. INTRODUCTION

Chronic myeloid leukemia (CML) is characterized by a reciprocal translocation between chromosomes 9 and 22, resulting Abl-proto-oncogene on chromosome 9 with Bcr (breakpoint cluster region) on chromosome 22 (1). The translocation will result in a fusion gene termed BCR-ABL or the Philadelphia chromosome that codes for a protein with excess tyrosine kinase activity (2) which deregulated cellular proliferation and development of growth factor independence, decreased adherence of the leukemic cells to the bone marrow stroma, and a reduced apoptotic response to mutagenic stimuli (3). The disease can pass into three distinct phases: The chronic phase (CP) followed by the accelerated phase and finally the blast phase. Most of the patients are commonly diagnosed in the CP (4). The only risk factors for chronic myeloid leukemia (CML) are: a). Radiation exposure: Being exposed to high-dose radiation (such as being a survivor of an atomic bomb blast or nuclear reactor accident) increases the risk of getting CML, b). Age: The risk of getting CML goes up with age and c). Gender: This disease is slightly more common in males than females, but it's not known why (5).

Allogeneic stem cell transplant has been used in the treatment of CML (3) and is the only curative therapy for CML; however, it bears a significant mortality risk. Age, disease status, disease duration, recipient-donor gender combinations, degree of histocompatibility between donor and recipient and the source of the transplant product have all been identified as significantly influencing long-term survival. Evidence in the pre imatinib era suggests that bone marrow transplant is best performed in the early phase of chronic CML (3-6), which reduced intensity conditioning treatments or non-myeloablative transplants have been proposed. This endeavors to produce graft-versus-leukemia effects without exposing the patient to the potential toxicity of conditioning treatments. Here, reconstitution of the immune system and associated anti-leukemia effect of the donor graft, compete against the growth of the malignancy. Preliminary data suggests that this approach may confer benefit, particularly in chronic phase CML (6). The BCR-ABL protein is an ideal drug target for CML treatment. Unique to leukemic cells, the BCR-ABL protein is expressed at high levels and its tyrosine kinase activity of the SH1 domain, which is essential for its ability to induce CML (7) as TK proteins are a broad group of cell membrane proteins (about 500 different proteins) involved in important cellular activities such as proliferation, differentiation, and apoptosis. TKIs are new and small designed targeted molecules that are analog to ATP molecule structure and arrive to compete with real ATP for binding to tyrosine part of TK molecule. Thus, they preclude TK phosphorylation via an inhibitory competitive replacement and cutting-off TK-dependent oncogenic pathways (8-9).

The incidence of overt thyroid dysfunction may depend on population iodine intake (10). The main causes of hypothyroidism in the developed world are Hashimoto's disease, and thyroid ablation (radioactive iodine, surgery, and drugs); and of thyrotoxicosis are Graves' disease in 70%, toxic multinodular goiter, and toxic adenoma. Subclinical thyroid dysfunction (commonly in women and the elderly population) is diagnosed more often because of widespread thyroid testing in modern clinical practice. Clear management strategies are however yet to emerge (11). Thyroid dysfunction, mostly hypothyroidism, is a well-recognized side effect of treatment with tyrosine kinase inhibitors (12-13). Its incidence ranged from 53% to 85% in retrospective and from 36% to 71% in prospective studies. Tyrosine kinase inhibitors (TKIs) block tyrosine kinase signaling pathways that modulate oncogenesis.2 They exhibit vascular and antiangiogenic properties by interacting with VEGF (14), which can be one of the Possible mechanisms causing thyroid dysfunction, beside the induction of a destructive thyroiditis (15-16-17), the inhibition of peroxidase activity (14), the blocking of iodine uptake (15), irreversible thyroid destruction (16), or capillary dysfunction (18-19).

II. MATERIAL AND METHOD

This cross sectional study involved 120 patients diagnosed with chronic myeloid leukemia; they were attended to Khartoum hospital of atomic and radiation therapy. Data collection via direct questionnaire included age, gender, duration of the disease and therapy used. Whole blood samples were collected under hygienic condition in heparinized containers, plasma used to measure thyroid function tests, T3, T4 and TSH by means of enzyme linked immunoassay (ELISA) method using fortress ^{TD} ELISA kits for TFT. Data analysis was performed by statistical package of social science (SPSS) program version 22.

III. RESULT

This cross sectional study involved 120 patients diagnosed with chronic myeloid leukemia; they were attended to Khartoum hospital to atomic and radiation therapy. 80 (66.7%), under treatment, their mean+SD of age was 41.35+16.5 years and duration of the disease 22.6+8.9 years and 40 (33.3%) were new cases and their mean+SD of age was 36.23+0.38 years and duration of the disease was 0.7+0.4 years. Considering home residence for those patients; 32 (27%) came from northern Sudan and the rest 78 (73%) from western Sudan.

TFTs measured were increased levels and when compared with reference ranges, each of them; T3, T4 and TSH brought significant difference, as p value for each was 0.000

Table 1: comparing of TFTs among CML patients with reference range

parameters	Mean±SD	reference range	P-value
T3	3.72±2.13	0.8-1.6 n/ml	0.000
T4	129.0±48.7	4.9-77 ug/dl	0.000
TSH	16.36±30.4	0.4-4.3 mIU/m	0.000

Significant difference p value less than 0.05

Considering the status of the CML, patients were two groups, new and under treatment groups, comparing TFTs among them showed that T3 and T4 and TSH gave significant difference for each (p value 0.00) as they were increased among under treatment group than new case one, in which all hormones were increased than the reference range as well. TSH among new case group revealed as in table 2

Table 2: comparing of TFTs among new case and under treatment CML patients

parameters	under treat Mean±SD	new case mean±SD	P-value
T3	2.79±1.19	5.58±2.36	0.000
T4	112.5±39.78	161.9±48.4	0.000
TSH	6.01±18.48	37.0±38.27	0.000

Significant difference p value less than 0.05

Considering gender, TFT between CML males and females did not differ, as they brought p value more than 0.05 as In table 3

parameters	male Mean±SD	females mean±SD	P-value
T3	2.75±1.11	2.82±1.28	0.739
T4	111.1±38.89	113.9±41.0	0.751
TSH	7.27±3.42	4.83±2.41	0.560

Significant difference p value less than 0.05

IV. DISCUSSION

Chronic Myeloid Leukemia (CML) is a clonal, myeloproliferative disease that develops when a single, pluripotential, hemopoetic stem cell acquires the Philadelphia chromosome. CML was the first hematological malignancy to be associated with a specific genetic lesion. First recognized in 1845, CML exhibits a consistent chromosomal abnormality in leukemic cells, identified in 1960 and termed the Philadelphia (Ph) chromosome (3).

Justifying thyroid dysfunction among CML patients under anti- proliferative drugs, one of them called Imatinib is the first generated tyrosine kinase Inhibitor, which prevents ATP binding to a specific situation of tyrosine kinase molecules that are involved in phosphorylation of membranous proteins and activation of the pathways that are necessary for tumor cell survey and proliferation. Therefore, tyrosine kinase inhibitor inhibits signaling proteins, which are responsible for tumor growth, invasion, angiogenesis and even metastasis. Although tyrosine kinase inhibitor are specific targeted-designed compounds, every agent interacts with many kinds of tyrosine kinases and produces many unwanted effects. One of the undesirable adverse effects is thyroid dysfunction. It has been have demonstrated that thyroid disturbances ranging from subclinical thyroid dysfunctions to overt clinically thyroid disorders during tyrosine kinase inhibitor therapy (21).

This study depended on if diagnoses of chronic myeloid leukemia has obvious effect on thyroid function tests, as new cases with no anti-leukemic drug were recruited beside old ones under treatment. Generally TFTs were increased among all leukemic patients when compared to the reference ranges of each hormone level. Comparing TFTs among new case group with under therapy group; also showed increased levels, but among treatment group TFT levels were massive high than new case patients. Gender has no effect on TFT levels, as they were increased among males and females and no significant difference was revealed. An agreement obtained by a Sudanese study aimed for evaluation of thyroid function tests while these patients diagnosed with CML and set for drugs anti to the proliferation drug and observing TFT among new cases as well. Thyroid dysfunction appeared to be related to the CML itself rather than be affected with significant difference more than those of under treatment, as variation revealed (20). Other study reached in disagreement of this study, as when measured TSH among both groups of CML patients, aimed to evaluate thyroid function at baseline and at 1, 3, 6 and 12 months after initiation of anti-proliferative drug therapy in 20 newly diagnosed BCR-ABL positive CML patients., 20 new cases with Philadelphia chromosome-positive CML without any underlying thyroid disorder or drug history interfering with anti-proliferative drug were enrolled. Thyroid function tests including serum TSH was assessed at baseline and during follow-up. TSH, during 1, 3, 6, and 12 months after initiation of anti-proliferative drug were not statistically significant change in thyroid function tests during treatment and all laboratory variables were in normal ranges (22). Other study reviewed all relevant studies regarding clinically approved TKIs, in respect to hypothyroidism as a side-effect, and to investigate the possible predictive value of hypothyroidism in patients taking these drugs. In order to identify studies regarding hypothyroidism as a side-effect of TKIs, a systematic PubMed/Medline literature Results: In USA 26 different TKIs were approved for use in clinical practice. According to some current studies, patients who develop hypothyroidism during TKI therapy have prolonged progression-free survival (23).

V. CONCLUSION

This study measured T3, T4 and TDH among chronic myeloid leukemia patients, they were attended for diagnoses and follow up, thyroid dysfunction was found among CML patients and they were increased among those under treatment more than new cases involved.

VI. RECOMMENDATION

In spite of the main purpose of applying anti-proliferative drug is to control CML, side effects of these drugs should be avoided and new version of treatment with less side effects needed.

REFERENCES

[1] Faderl S, Talpaz M, Estrov Z, O'Brien S, Kurzrock R, Kantarjian HM. The biology of chronic myeloid leukemia. New Engl J Med. 1999;341(3):164–72.
[2] Bedi A, Zehnbauer BA, Barber JP, Sharkis SJ, Jones RJ. Inhibition of apoptosis by BCR-ABL in chronic myeloid leukemia. Blood 1994;83:2038-44.
[3] Goldman JM, Melo JV. Chronic myeloid leukemia - advances In biology and new approaches to treatment. New Engl J Med. 2003;349(15):1451–64.
[4] Sessions J. Chronic myeloid leukemia in 2007. J Manag Care Pharm 2007;13:4-7
[5] American Society of Clinical Oncology. Leukemia - Chronic Myeloid - CML: Treatment Options. 11/2016.
[6] Melo JV, Hughes TP, Apperley JF. Chronic myeloid leukemia. Hematology. 2003;17(1):132–5
[7] Druker BJ, O'Brien SG, Cortes J, Radich J. Chronic myelogenous leukemia. Hematology. 2002;(1):111–35.
[8] Daub H. Kinase inhibitors: narrowing down the real targets. Nat Chem Biol. 2010 Apr;6(4):249-50
[9] Rios MB, Ault P. Identification of side effects associated with intolerance to BCR-ABL inhibitors in patients with chronic myeloid leukemia. Clin J Oncol Nurs. 2011;15(6):660-7.
[10] Bulow Pedersen I, Knudsen N, Jorgensen T. et al Large differences in incidences of overt hyper and hypothyroidism associated with a small difference in iodine intake: a prospective comparative register based population survey. J Clin Endocrinol Metab 2002 874462–4469.
[11] Sato K, Okamura K, Hirata T. et al Immunological and chemical types of reversible hypothyroidism; clinical characteristics and long-term prognosis. Clin Endocrinol 199645519–524
[12] Hershman JM, Liwanpo L 2010 How does sunitinib cause hypothyroidism? Thyroid 20:243–244.
[13] Torino F, Corsello SM, Longo R, Barnabei A, Gasparini G 2009 Hypothyroidism related to tyrosine kinase inhibitors: an emerging toxic effect of targeted therapy. Nat Rev Clin Oncol 6:219–228.
[14] Le Tourneau C, Faivre S, Raymond E. New developments in multitargeted therapy for patients with solid tumours. Cancer Treat Rev. 2008;34(1):37-48
[15] Desai J, Yassa L, Marqusee E, George S, Frates MC, Chen MH, Morgan JA, Dychter SS, Larsen PR, Demetri GD, Alexander EK 2006 Hypothyroidism after sunitinib treatment for patients with gastrointestinal stromal tumors. Ann Intern Med 145:660–664.
[16] Faris JE, Moore AF, Daniels GH 2007 Sunitinib (sutent)- induced thyrotoxicosis due to destructive thyroiditis: a case report. Thyroid 17:1147–1149.
[17] Grossmann M, Premaratne E, Desai J, Davis ID 2008 Thyrotoxicosis during sunitinib treatment for renal cell carcinoma. Clin Endocrinol (Oxf) 69:669–672.
[18] Wong E, Rosen LS, Mulay M, Vanvugt A, Dinolfo M, Tomoda C, Sugawara M, Hershman JM 2007 Sunitinib induces hypothyroidism in advanced cancer patients and may inhibit thyroid peroxidase activity. Thyroid 17:351–355.
[19] Mannavola D, Coco P, Vannucchi G, Bertuelli R, Carletto M, Casali PG, Beck-Peccoz P, Fugazzola L 2007 A novel tyrosine-kinase selective inhibitor, sunitinib, induces transient hypothyroidism by blocking iodine uptake. J Clin Endocrinol Metab 92:3531–3534.
[20] Hossein Rahimi; Zahra Mazloum Khorasani; Saeedeh Shariati. Does thyroid dysfunction happen in CML patients receiving Imatinib for treatment? Article 9, Volume 2, Issue 2, Spring 2015, Page 92-95
[21] Nawal K. Mustafa et al. The impact of tyrosine kinase inhibitors on thyroid function tests among Sudanese patients with chronic myeloid leukemia. International Journal of Current Research, Vol. 10, Issue, 01, pp.63979-63983, January, 2018.
[22] Abolghasem Allahyari , Foroogh Salehi , Mostafa Kaboli , Masoud Sadeghi. Evaluation of Thyroid Dysfunction during Imatinib Therapy in Chronic Myeloid Leukemia. Iranian journal for blood and cancer Volume 8 | Issue 1 | March 2016 .
[23] T Davor Kust , Marin Prpić , Ivan Kruljac , Ante Bolanča , Zvonko Kusić. yrosine kinase inhibitors and hypothyroidism - an intriguing link. Endocrine Oncology and Metabolism. : June 15th 2016.

Table 3.6 shows that there is no association between duration of treatment and age of patient and T3,T4,and TSH levels in patients with CML

Parameters	Male (Mean±SD) n-15	Female (Mean±SD) n-25	P-value
T3 (ng/ml)	5.73±2.40	5.49±2.39	0.762
T4 (ug/dl)	162.5±50.6	161.7±48.2	0.961
TSH (IU/ml)	29.8±18.24	41.4±20.41	0.352

Table 3.7 shows that there is no association between duration of treatment and age of patient and T3,T4,and TSH levels in patients with CML.

Parameters	Mean ± SD				P-value
	N-Sudan	C-Sudan	W-Sudan	E-Sudan	
T3 (ng/ml)	2.71±0.74	2.40±0.88	2.92±1.36	1.92±0.96	0.353
T4 (ug/dl)	118.2±33.6	107.0±33.6	108.8±43.2	135.5±37.9	0.521
TSH (IU/ml)	2.03±1.37	2.19±1.77	8.31±3.12	3.12±3.15	0.562

Table 3.8 shows that there is no association between duration of treatment and age of patient and T3,T4,and TSH levels in patients with CML.

Parameters	Mean ± SD			P-value
	N-Sudan	C-Sudan	W-Sudan	
T3 (ng/ml)	5.17±1.96	5.48±3.49	5.79±2.29	0.778
T4 (ug/dl)	151.7±54.2	167.0±46.3	165.6±47.6	0.721
TSH (IU/ml)	28.8±25.1	39.6±31.1	40.3±35.1	0.619

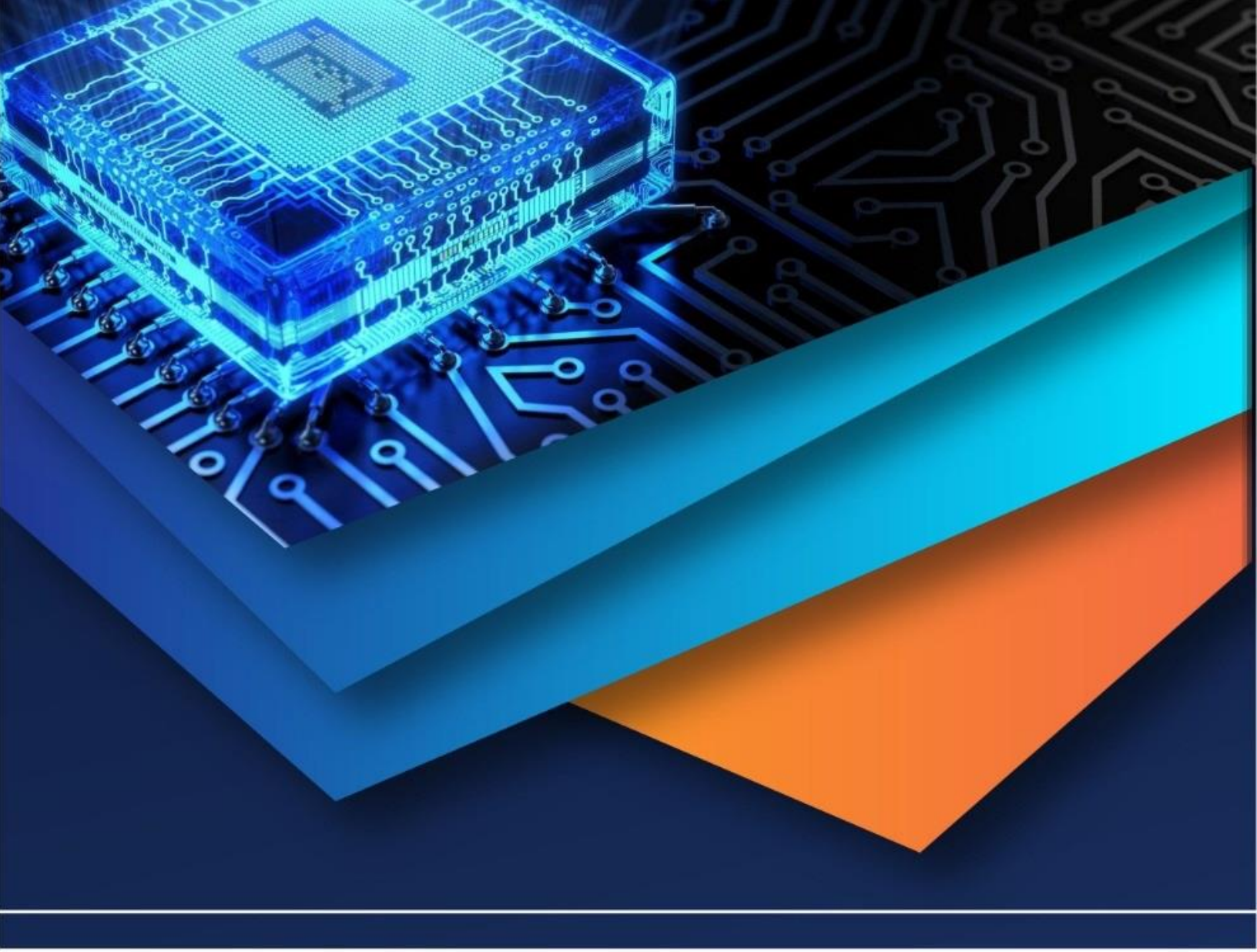
Table 3.9 shows that there is no association between duration of treatment and age of patient and T3,T4,and TSH levels in patients with CML.

Parameters		Age	Duration (Month)
T3 (ng/ml)	R-value	-0.148	-0.083
	P-value	0.189	0.462
T4 (ug/dl)	R-value	-0.076	-0.195
	P-value	0.503	0.084
TSH (IU/ml)	R-value	0.037	-0.154
	P-value	0.745	0.174

Table 3.10 shows that there is no association between duration of treatment and age of patient and T3,T4,and TSH levels in patients with CML.

New case

Parameters		Age	Duration (Month)
T3 (ng/ml)	R-value	-0.011	0.017
	P-value	0.947	0.919
T4 (ug/dl)	R-value	-0.122	0.190
	P-value	0.455	0.241
TSH (IU/ml)	R-value	-0.134	-0.181
	P-value	0.409	0.263



10.22214/IJRASET

45.98

IMPACT FACTOR: 7.129

IMPACT FACTOR: 7.429

INTERNATIONAL JOURNAL FOR RESEARCH

IN APPLIED SCIENCE & ENGINEERING TECHNOLOGY