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Hematological events and thyroid status in Imatinib treated CML Iraqi

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Abstract:

Background: Chronic myeloid leukemia (CML) is myeloproliferative of hematopoietic stem cells resulting in marked increased in granulocytes, platelets and red cells.
Imatinib mesylate (IM) is potent tyrosine kinase inhibitor acts by occupying ATP binding site for BCR-ABL oncoprotein preventing phosphorylation of substrate and interrupting contact with protein.
Aim of study: Evaluation of thyroid function and myelosuppresion induced by IM in CML patients.
Materials and Methods: The study enrolled 13 patients with CML treated by IM for more than 6 months. Total blood count and blood film and thyroid function.
Tests (T1 ,T4 and TSH) were performed.
Results: All patients belong to Grade3 and Grade2 only of mylosuppresion, the most common cytopenia is neutropenia in (7) patients, anemia in (5) patients and only (4)patients having thrombocytopenia. Only three patients don't achieve remission (6.6 %).Regarding thyroid function only one patient has high TSH level with normal T1 and T4. In spite of TSH level in patients significantly higher than the control group the mean values of two group were within normal range. Non-significant difference in T1 and T4 between the control and patients groups.
Conclusion: IM do not seem to has clinically significant effect on thyroid function. However, thyroid function test is indicated before initiated of treatment with IM. Also CBC is highly recommended for monitoring CML patients on IM.

Keyword: *CML, Thyroid function, Imatinib.*

Introduction:

Chronic myeloid leukemia (CML) is myeloproliferative disorder of hematopoietic stem cells resulting in marked increased in granulocytes, platelets and red blood cells. CML is characterized by Philadelphia (ph) chromosome. It is the product of reciprocal translocation between the long arms of chromosome 6 and 22.

This reset is fusion gene BCR-ABL that encodes to abnormal protein tyrosine kinase activity (1,2,3).

Imatinib mesylate (IM) is potent inhibitor of tyrosine kinase, including c kit platelets- derived growth factor receptor (PDGF-R), BCR-ABL.

This drug was used for the first in 3661 in patients with CML resistant α- interferon where show to re establish normal hematopoiesis (Ph negative).

The mechanism of action of IM is by occupy ATP binding site for BCR- ABL oncoprotein preventing phosphorylation of substrate and interrupting contact with protein. (4,5,6).

Myelosuppression developed during IM treated of CML is common(7).

The wide use of tyrosine kinase inhibitors raised the awareness of side effects on thyroid function. The effects of IM on multiple endocrine glands are now recognized that may have impaction on quality of life in CML patients on IM.

In general IM side effects are fatigue, peripheral and periobital oedema . these signs are undistinguishable for hypothyroidism.

Few previous studies about thyroid function in IM treated CML patients that had onflicting results(36).

The aim of our study is to evaluate thyroid function and toxic thyroid effect for IM on CML patients more them 6 months of treated.

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Material and method:

The present study was retrospective, observational conducted on 13 patients of CML (31 male and 31 female) in chronic phase attending national center of hematological disease.

This study was conducted from Feb 2135 to Oct.2135. The diagnosis of all included patients was confirmed by real time PCR for BCR-ABL fusion transcript.

All patients were on Imatinib for 6 months or more 411 mg daily. Patients with other comorbidities like liver diseases, renal disease or endocrine disease were excluded from this research.

Hematological remission is defined as platelets count < 451 x31 /L, WBC count below 31 X 316/L basophils below 5 % with no immature cells in blood.

A venous blood were obtained from each patients 2 ml in EDTA tubes for peripheral blood findings (red cell indices WBC and differential and platelet count)using hematology counter (Mindray 1111) with blood film staind by Giemsa stain., and 2 ml in gel tubes to gel serum where thyroid function was evaluated (TSH , T1 and T4) performed using chemo-radiolumnces Tosoh AIA-161 (Japan).

Ethical approval were performed by local committee in the national center of hematological diseases.

Adverse events:

The adverse events were graded according to the national cancer institute (NCI) common terminology criteria for adverse events (CTCAE)(1).

Table (1) showed the grades of adverse events

Adverse reaction	Grade 3	Grade 2	Grade 1	Grade 4
Anemia	Hb<LLN to g/dL 31.1	Hb<31.1 g/Dl to 1.1 g/dL	Hb<1.1 g/dL transfusion ; indication	-Life ;threatening urgent intervention indicated
Neutropenia	Neutrophils<LL N to 3511/mm^1	Neutrophils mm^1/3511> 1 to 3111/mm	Neutrophils mm^1/3111> to 511 mm^1	Neutrophils mm^1/511>
Thrombocytopeni a	*Platelets <LLN to 75,111/mm^1	mm/75,111> 1 to mm^1/51,111	mm/51.111> 1 to mm^1/25,111	mm/25,111> 1

*** LLN lower limit of normal.**

Statistical analysis :

The statistical significant of difference between the two groups examined were evaluated by student t- test. The level of significant was of 1.15.

Results :

Table (2): showed thyroid function tests in CML patients and control group.

	Controls	Patients	P-value
TSH	1.64 ± 3.44	3.2 ± 2.2	1.12
T4	2 ± 7.33	2.63 ± 6.66	.N.S
T1	1.614 ± 3.166	1.44 ± 3.34	.N.S

P< 1.15 significant.
N.S: Means non-significant.

The outcome of treatment with IM showed that only three patients (6.6 %) do not achieved hematological remission. Two patients with thrombocytosis platelets count more than 451 X 316/L and the third patient had neutrophilia with platelets more than 451 X 316/L

The grade of cytopenia are belong to grade one and grade two only. No patients was found on grade 1 or grade 4.

The most common cytopenia is neutropenia 7 patients (22.52) while patients suffered from anemia were five (36.3 %) and four patients had thrombocytopenia (32.6 %) as shown on table (3).

Regarding the thyroid function tests. Only one patients (1.22) has TSH above normal but below 31 mIU/ml with normal T1 and T4 values.

The TSH is level significantly more than the control group although the mean levels of both the patients group and control group were within normal limit. Non significant difference in the values of both T4 and T1 between the patients and control groups were noticed as shown on table (2).

Table(3):Showed grades of cytopenia and number of patients having cytopenia.

Cytopenia	Grad 3	Grad 2	Grad 1	Grad 4	Over all (%) percentage
Neutropenia	5	2	1	1	(% 22.5) 7
Thrombocytopenia	4	1	1	1	(% 32.6) 4
Anemia	2	1	1	1	(% 36.3) 5

Myelosuppresion developing during IM treatment of CML is common . It is due to combined effect of suppression of leukemic clone and inhibition of normal hematopoiesis . Our data clearly revealed that the suppression related to grade 3 and 2 only as shown on table (1).

The myelosuppresion is always limited to the first few weeks of treatment. So the incidence of grade 1 and 4 of myelosuppresion is predominant at initiation of treatment and decrease with longer time after exposure to IM .

This could be explained that our patients had more than 6 months on IM treatment. Finally the hematological side effect is dose dependent and reversible (6, 31).

Hematological toxicity is very important in modifying treatment discontinuation, dose reduction to avoid death caused by bleeding or infection (33,32,31).

Therefore the management of cytopenia lies mainly on tight monitoring of full blood counts.(34)

It is difficult to compare our data with other published studies about the incidence of all grade of cytopenia because it varies from 2 to 61 % which is very wide range that is difficult to interpret(35).

Identifying thyroid disease in CML patient can be difficult CML patients but may had important consequences many of symptoms of hypothyroidism like fatigue , leg oedema , peripheral odema can be attributed to CML symptoms or to drug side effects or thyroid dysfunction(36).

In spite of our results identifying statistically difference in TSH levels between CML treated patients with IM and control this change was within normal laboratory values.

Moreover, Only one patients has subclinical hypothyroidism that is clinically not important nearly similar finding by Dora et.al. who examined 61 patients with CML treated by IM

61 out 61 patients have normal thyroid function(37). Ghalaut et.al. study from India 6 month follow up of 11 patients treated with IM only two patients had subclinical hypothyroidism(31).

Mashhadi in 2134 prospective study on 36 patients. All patients are within normal value of thyroid function after treatment with IM(36).

However, Kim et.al. reported that 252 of CML patients receiving IM had thyroid dysfunction(21).

It was suggest that the mechanism of sub-clinical hypothyroidism was stimulation of both T4 and T1 clearance due to increase activity of microsomal enzymes of the liver.(23)

The management of subclinical hypothyroidism is still controversy. However, the existence of hypothyroidism in IM treated patients do not need to stop treatment or reduction of the dose of IM.

In spite of, the normal thyroid function in IM treated CML patients thyroid function test should be performed before initiation of IM treatment.

Conclusion:

IM do not seem to has clinically significant effect on thyroid function. However, thyroid function test is indicated before initiated of treatment with IM. Also CBC is highly recommended for monitoring CML patients on IM.

Recommendations:

3.Larger number of CML patients on IM needed to evaluate their thyroid function.

2.Thyroid function to be evaluated on CML patients on Nilotinib.

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References:

1. lies led JL ,Lichtman MA. (2010) Chronic myelogenous leukemia and related disorders In: Kaushanksy K, Lichtman MA, Beutler E, Kipps TJ, Seligsohn U, Prchal JT, editors. Williams Hematology. New York :McGraw- Hill: 1331 -1379
2. Kavalerchik E, Goff D , Jamieson Ch(2008) chronic myeloid leukemia stem cells J. Clin. Oncol. 26: 2911 -2915.
3. Savonarola M. Talas Me.(2008) Getting to the stem of chronic myeloid leukemia . Nay. Rev. Cancer 8: 341-350
4. Garcia-Manero G. Feel S. Orientation S.(2003) chronic myelogenous leukemia , review and update of therapeutic strategies Cancer 98:437-457.
5. daub H.(2010) Kinase inhibitors:narrowing dawn the real targets. Nat Chem Biol. 6:249-250.
6. Illouz F. Laboureau-Soares S. Dubois(2009)tyrosine Kinase inhibitors and modifications of thyroid function tests:areview.European J Endocrino..160:331-336.
7. Baccarani M. Cortes J. Pane F. Niederwieser D. Saglio G. (2009) chronic myeloid leukemia An update of concepts and management recommendations of European leukemia net J.clin.Oncol. 27:6041-6051.
8. Kantaarjian H.Talpaz M. O Brien S. ,Garcia -Manero G.(2004) high dose imatinibmesylateTherapy in newly diagnosed ph+ chronic phase CML 103: 2873-2878.
9. NCCN . Chronic myelogenous leukemia . NCCN clinical practice Guidelines in OncologyVersion 3: (2013).
10. SteegmannJL ,Baccarani M., Breccia M., Casado LF (2016) European leukemia Net recommendation for the management and avoidance of adverse events of treatment in CMLLeukemia 30 , 1648- 1671.
11. Sneed TB, Kantarjian HM. Talpaz M. (2004) The significance of myelosuppresion during therapy with imatinibmesylate in patients with CML in chronic phase Cancer 100 : 116-121.
12. Steegmann JL. Cervantes F. IeCoutre P. Porka K. (2012) Off-target effects of BCR-ABL inhibitors and their potential long term implications in patients with CML Leukemia lymphoma53: 2351 - 2361 .
13. RostiG. ,Castagenetti F. ,Gugliotta G., Palandri F. (2012) physicians' guide to the clinical management of adverse events on nilotinib therapy for the treatment of CML . Cancer treatment review 38: 241 -248.
14. Baccarani M., Deeininger MW., Rosti G., Hochhaus A.(2013) European leukemia Net recommendations for the management of CML Blood :122:872- 884.
15. Bilen Y,,Erdem F.(2012) Hematologic, cytogenetic ,and molecular responses to imatinib therapy for CML a single - center experience in Turkey . Turk. Med. Science.42(1) 31-38.
16. Illoux, F. SoaresS.,Dubois S. Rohmer, V.(2009) Tyrosine kinase inhibitors and modifications of thyroid function tests : a review 160: 331-336.
17. Dora JM.,Leie, MA. Neto B.(2008)Lack of imatinib induced thyroid dysfunction in a cohort of nonthyriodactomized patients Europe j. Endocrinology. 158-171.
18. Ghalaut VS, Prakash G., Bala M. (2013) Imatinib and thyroid dysfunction in BCR-ABL positive CML patients. Am J. Cancer Therap. Pharma. 1: 1-7.
19. Mashhadi M., Kaykhaei M., Mohammadi M., Hashemi M. Fatide T.(2014) Imatinib therapy in CML and thyroid function tests Inter. J. Of Hemat.Onco. And stem cell research vol 8 No.320-23.
20. Kim TD, Schwarz M.,Nogai H.,(2010) thyroid dysfunction caused by second-generation tyrosine kinase inhibitors in Ph positive CML. Thyroid 20:1209-1214.
21. de Groot JWB ,Zonnenberg BA, Plukker JT.(2005) imatinib induces hypothyroidism in patients receiving levothyroxine. Clin. Pharm. Therap. 78: 433-438.

التأثيرات الجانبيه وحاله الغده الدرقيه في مرضى أبيضان الدم المزمن الحبيبي العراقيين تحت علاج ايماتنب

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الخلاصه:

ان مرض أبيضان الدم الحبيبي المزمن هو اضطراب الخلايا الجذعية الدمويه مما ينتج عنها زياده كبيره في كريات البيض الحبيبيه وأقراص الدم والكريات الحمراء،

يعتبر عقار ايماتنب ماسيليت مثبط فعال لإنزيم تايروسين كاينيز وذلك من خلال منع جزءيه ATP من الالتصاق بالبروتين المسرطن واكمال عمليه الفسفره .

تهدف الدراسه الى تقييم وظائف الغده الدرقيه ومدى تثبيط انتاج خلايا الدم من قبل عقار ايماتنب في مرضى ابيضاض الدم الحبيبي المزمن في العراقيين

تضمنت الدراسه (31) مريضامصابين بابيضاض الدم الحبيبي المزمن في حالته المزمنة عولجوا بعقار ايماتنب لمده سته أشهر فاكثر . تم اجراء صوره الدم الكامله وفحوصات وظائف الغده الدرقيه (T3 , T4 , TSH) .

أظهرت النتائج بان كل المرضى ينتمون الى الدرجه الاولى والثانيه في مستوى تثبيط انتاج خلايا الدم والأكثر شيوعا (7) مرضى ماتصبون بنقص انتاج كريات الدم البيض الحبيبه و خمس مرضى بفقر الدم وأربع مرضى يعانون من نقص في الأقراص الدمويه .وهنالك ثلاث مرضى فقط (9.6%) لم يصلو بعد الى مستوى الافاقه من المرض.

وبخصوص الغده الدرقيه تبين وجود مريض واحد فقط لديه (TSH) فوق المستوى الطبيعي مع مستوى طبيعي لكل من T4 و T3.

وجد هنالك فارق معنوي اعلى في TSHفي مجموعه المرضى مقارنه بمجموعه السيطره ولكن المعدل ضمن الحدود الطبيعية للفحص.

تبين ان عقار ايماتنب لا يؤثر سريريا على وظائف الغده الدرقيه ومع ذلك ينصح بإجراء فحوصات الغده الدرقيه قبل البدء بالعلاج وكذلك صوره الدم مهمه جدا في مراقبه المريض اثناء العلاج