Dissertation on

"THYROID DYSFUNCTION CAUSED BY TYROSINE KINASE INHIBITORS IN PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA"

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CERTIFICATE

This is to certify that the dissertation titled "**THYROID DYSFUNCTION CAUSED BY TYROSINE KINASE INHIBITORS IN PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA**" is the bonafide original work of **Dr. M. AMARAVATHI** in partial fulfillment of the requirements for M.D. Branch – I (General Medicine) Examination of the Tamilnadu DR. M.G.R Medical University to be held in APRIL 2016. The Period of study was from October 2014 to September 2015.

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DECLARATION

I, **Dr.M.AMARAVATHI** solemnly declare that dissertation titled "**THYROID DYSFUNCTION CAUSED BY TYROSINE KINASE INHIBITORS IN PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA**" is a bonafide work done by me at Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai-3 during October 2014 to September 2015 under the guidance and supervision of my unit chief **Prof. S. G.SIVA CHIDAMBARAM M.D**, Professor of Medicine, Madras Medical College and Rajiv Gandhi Government General Hospital, Chennai.

This dissertation is submitted to Tamilnadu Dr. M.G.R Medical University, towards partial fulfillment of requirement for the award of **M.D. Degree (Branch – I) in General Medicine – SEPTEMBER 2015.**

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INTRODUCTION

INTRODUCTION

Chronic myeloid leukemia known as chronic myelogenous leukemia, chronic granulocytic leukemia is clonal disease that results from an acquired genetic change in a pluripotential haemopoietic stem cell. This altered stem cell proliferates and generates a population of differentiated cellsthat gradually displaces normal haemopoiesis and leads to greatly expanded total myeloid mass. One important landmark in the study of CML was the discovery of the Philadelphia chromosome in 1960; another was the characterization in the1980s of the *BCR–ABL* chimeric gene and associated oncoproteinand a third was the demonstration that introducing the *BCR–ABL* gene into murine stem cells in experimental animalscaused a disease simulating human CML.

Until the 1980s, CML was generally assumed to be incurable and Was treated palliatively – in the early days with radiotherapy, And more recently with alkylating agents, notably busulphan. CML Can be permanently eradicated in the majority of patients who Survive after haemopoietic stem cell transplantation (SCT), but The proportion of patients eligible for SCT is still relatively small. The introduction into clinical practice of imatinib in 1998 was An important therapeutic advance, as with this agent most patients Achieve a complete cytogenetic response and may expect prolongation

of survival compared with other methods of treatment Epidemiology, etiology and natural history : The incidence of CML appears to be constant worldwide. Itoccurs in about 1.0–1.5 per 100 000 of the population perAnnum in all countries where statistics are adequate. CML is rarebelow the age of 20 years

But occurs in all decades of life, with a Median age of onset of 50–60 years. The incidence is slightly higher in males than in females. The risk of developing CML is slightly but significantly Increased by exposure to high doses of irradiation, as occurred in survivors of the atomic bombs exploded in Japan in 1945, and inpatients irradiated for ankylosing spondylit is but, in general, almost all cases must be regarded as ‘sporadic’ and no predisposing factors are identifiable. Clinically, CML is biphasic or triphasic disease that is usually diagnosed in the initial ‘chronic’, ‘indolent’ or ‘stable’ phase and then spontaneously evolves after some years into an advanced phase, which can sometimes be subdivided into an earlier accelerated Phase and a later acute or blastic phase.

There has been much debate about the duration of disease before the diagnosis is established, a question that is essentially unanswerable. If It is assumed that the disease starts with a ‘transforming event’ occurring in a single stem cell, it could be 5 –10 years before the

Disease becomes clinically manifest. This estimate depends onassumption that the leukocyte doubling time in the prediagnosis Phase is not fundamentally different from the doubling time after diagnosis and the observation that the latent interval between exposure to irradiation. From atomic bombs and the earliest identifiable increased incidenceof CML was about 7 years. One study concluded that routine blood count might have identified CML on average 6 Months before it was actually diagnosed in individual patients. Patients are usually in the ‘chronic’ phase when CML is diagnosed. This chronic phase lasts typically 2–7 years but it May seen in rare cases, last more than 15 or even 20 years. Even more Rarely, spontaneous remissions have been described. In about one-half of cases the chronic phase transforms unpredictably And abruptly to a more aggressive phase that used to be referred to as ‘blastic crisis’ and is now usually described as acute or blastic transformation. In the other half of cases, the disease evolves somewhat more gradually, through an intermediate phase described as ‘accelerated’ phase, which may last for months or Years, before frank blastic transformation supervenes, which May have myeloblastic or lymphoblastic features. Occasional Patients have a disease that progresses gradually to a myelofibrotic orosteomyelosclerotic picture that is characterized by extensive Marrow fibrosis and sometimes gross overgrowth of

Bonytrabeculae; the clinical problems are then usually due to Failure of haemopoiesis rather than to blast cell proliferation, but a predominantly blastic disease can still supervene. The duration of survival after onset of transformation is usually 2–6 months. Chronic myeloid leukemia is a common proliferative disorder of myeloid series results in leucocytosis,basophils,immature granulocytes, anemia, thrombocytosis and splenomegaly. In hematopoetic stem cell BCR-ABL a fusion gene formed from reciprocal translocation of chromosome 9 and 22.

Tyrosine kinase inhibitors belongs to molecular targeted therapies .Acts by blocking the signaling pathways which helps in modulatingoncogenesis. Targets include anti angiogenic properties and vascular properties against VEGFR, PDGFR, RET, KIT which are involved in tumor formation. Multi targeted therapies include sunitinib, imatinib, sorafinib, motesanib are tyrosine kinase inhibitors Targeted at different sites of BCR ABL gene.

AIMS

AND

OBJECTIVES

AIMS AND OBJECTIVES

To investigate the effect of tyrosine kinase inhibitors on thyroid function.

REVIEW

OF

LITERATURE

REVIEW OF LITERATURE

Chronic myeloid leukemia is the first malignancy in humans with a specific Genetic lesion, BCR-ABL oncogene harbored by Philadelphia chromosome. Since then, it is known for discovery of targeted therapeutics and molecular mechanisms in field of hematological malignancies. Chronic myeloid leukemia resulted as acquired genetic change in a pleuripotent haemopoietic stem cell. This altered stem cell " proliferates and generates a population of differentiated cells that gradually displace normal haemopoiesis and leads to increase expansion of total myeloid mass. In the study of CML, the first most important discovery is Philadelphia (Ph) chromosome in 1960. Secondly, description of BCR–ABL chimeric gene and oncoprotein in 1980. Thirdly, In experimental animals, introduced an BCR-ABL gene in to the Murine stem cells Whichstimulated Chronic myeloid leukemia.

As it is a clonal hematopoietic stem cell disorder. Accumulation of mature myeloid cells in blood and bone marrow progressively. Due to*BCR-ABL1* chimeric gene product, which is an active tyrosine kinase, resulting inreciprocal translocation between the long arms of chromosomes9 and 22 t(9;22) (q34;q11).

Cytogenetically detected as the Philadelphia chromosome. CML constitutes 15% of all cases of leukemia. Male:Female ratio is 1.6:1 Reportedas Male predominance.DiagnosisOf CML median age Considered as 55 to 65 years.CML is Less common in children; accounts 3% of patients below 20 years. Incidence of CML slowly increasing with age. Peak incidence increases after the 40 to 50years Ofage. In CML annual incidence is 1.5 cases per 100,000 individuals.

Multiple studies shows that the incidence of CML over several decades has not changed. In worldwide, Incidence was reported about 100,000 cases annually. Almost all cases must be Considered as ‘sporadic’, in which predisposing factors are not identified .In particularly, there is no familial predisposition and no definite association with HLA genotypes.An infectious agent has no contribution in etiology. No increase risk inmonozygotic twins.Etiologic agents Such as benzene fertilizers, insecticides, viruses, secondary to chemotherapy of other malignancies, radiation and other toxins are also not associated with etiology of CML.

It has reported that ionizing radiation exposuresin nuclear accidents, Malignancies like Cervical cancer those are treated with radiation. Rheumatologic condition like few cases of ankylosing

spondylitis treated with radiation therapy has increased the risk of CML, it is related to 5–10 years of exposure and also it is dose-related. Median age of exposure reported as 6.5yrs.Among survivors of atomic bomb explorers in Japan 1945, Risk of developingCMLIs slightly increased. Chronic myelogenous leukemia include "BCR rearrangement - positive CML, Chronic monocytic leukemia, chronic myelomonocytic leukemia, chronic eosinophilic leukemia, juvenile myelomonocytic leukemia and chronicneutrophilic leukemia."

BCR rearrangement-positive CML indicates increased granulocytosis, Anemia,large proportion of mature neutrophils, splenomegaly more commonly, normal or elevated platelet counts, and absolutebasophilic. The hyper cellularmarrow contains 90% of Philadelphia chromosome by cytogenetic analysis. By molecular diagnosticanalysis, BCR gene on chromosome 22 is rearranged in 95 % of cases approximately.

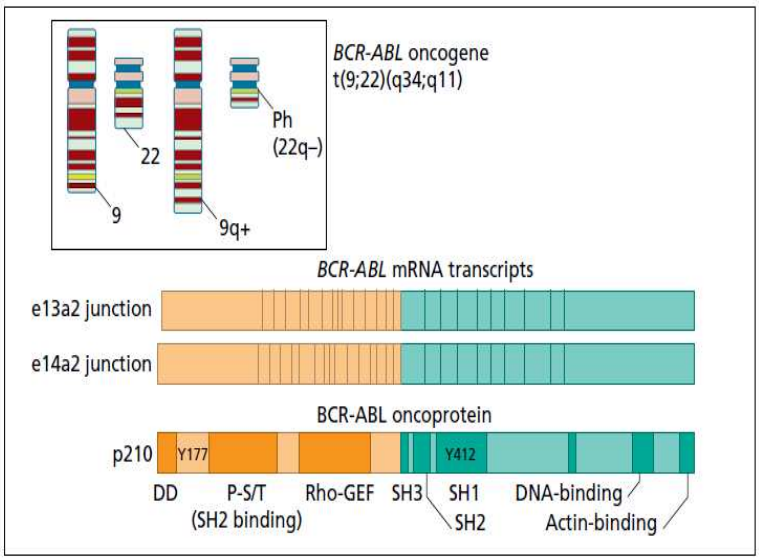


Figure 37.2 The t(9;22) translocation and its products: the *BCR–ABL* oncogene on the Ph chromosome and the reciprocal *ABL–BCR* on the derivative $9q^+$ chromosome. In classic CML, *BCR–ABL* is transcribed into mRNA molecules with e13a2 or e14a2 junctions, which are then translated into the $p210^{BCR-ABL}$ oncoprotein. This oncoprotein is a hybrid containing functional domains from the N-terminal end of BCR [dimerization domain (DD)], SRC-homology 2 (SH2)-binding and the Rho GTP–GDP exchange-factor (GEF) domains and the C-terminal end of ABL. [Only SRC-homology regions 2, 3 and 1 (SH2, SH3 and SH1 respectively) and the DNA- and actin-binding domains are shown.] Tyrosine 177 (Y177) in the *BCR* portion of the fusion gene and tyrosine 412 (Y412) in the ABL portion are important for the docking of adapter proteins and for BCR–ABL autophosphorylation respectively. P-S/T denotes phosphoserine and phosphothreonine.

"*ABL* proto-oncogene, an non-receptor tyrosine kinase, located on chromosome 9 was translocated to chromosome 22. The positions of the genomic breakpoint on chromosome 22 in different CML patients". Translocation of Ph causing 5′- sequences from *BCR* gene juxtaposed with 3′-ABL Sequence which is derived from chromosome 9 .Transcription of BCR-ABL, an 8.5kbm RNA encoding protein which has molecular Weight of 210 KDa. Tyrosine kinase activity is far more in p210 BCR-ABL Compared to normal *ABL* gene product. BCR–ABL transcript has two variants. It depends on break in introns between the exons e13 and e14 of which results in e13a2 mRNA junction or break in intron between the exons e14 and e15 of which resulted in

e14a2 mRNA.

In CML Patients, the transcription of BCR-ABL has no significant prognosis. Expression of *ABL–BCR* gene der9q location constitute 70%. prognosis does not depend on expression present or absent.*BCR–ABL* gene formed from thefusion of the *BCR* gene first exon with the *ABL* gene Second exon.Though, B-cells , NK cells, Tcells have BCR-ABL and Ph chromosome butmost Of the Bcells and all Tcells progenitors of leukemic clone undergo apoptosis leaving behind unaffected cells.

Colony forming cells of positive Ph chromosome binds to Fibronectin is less compared to normal. Due to Modification of CD15 antigens resulted in p-select in binding to receptors in CML Granulocytes. In the BCR Gene of first intron, genomic break point occurs in 2/3rd of patients with Ph positive ALL patients. In very rare instances, Ph chromosome found to be associated with chronic neutrophilic leukemia and instead of P210, In CML Patientsp190 Protein is present. Experimental studies showed that when BCR-ABL gene has cloned and introduced in to Retroviral vector, in Which this vector transfected into Murine Hematopoietic stem cells and these stem cells have produced a disease in mice which Mimics CML. Pathogenesis include Autophosphorylation of intracellular proteins. Like crkl, Mek1/2, Racand Jnk Where this mechanism does nothappens normally. Due to activation of intracellular

proteins results in signal transduction pathways of STAT, RAS. Another mechanism, P13 kinase- AKT pathway stimulation resulted in Apoptosis. Thus in targeted stem cells programmed cell death activated by BCR-ABL gene.

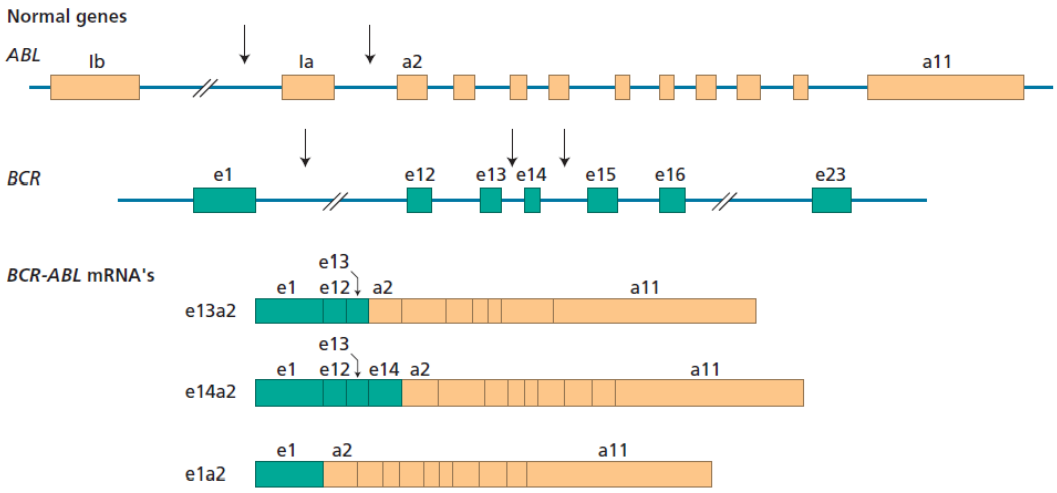


Figure 37.3 The structure of the normal *BCR* and *ABL* genes and the fusion transcripts found in CML and Ph-positive ALL. The ABL gene contains two alternative 5'-exons (named Ib and Ia) followed by 10 'common' exons numbered a2 to a11 (orange boxes). Breakpoints in CML and Ph-positive ALL usually occur in the introns between exons Ib and Ia or between exons Ia and a2 (as shown by vertical arrows). The *BCR* gene comprises a total of 23 exons, 11 exons upstream of the M-BCR region, five exons in the M-BCR that were originally termed b1 to b5 and are now renamed e12 to e16, and seven exons downstream of M-BCR. For convenience, only exons e1, e12 to e16 and e23 are shown. Breakpoints in CML usually occur between exons e13 (b2) and e14 (b3) or between exons e14 (b3) and e15 (b4) of the M-BCR (as shown by two vertical arrows placed centrally). The majority of patients with Ph-positive ALL have breakpoints in the first intron of the gene (between e1 and e2 (not shown), arrow at left). Three possible BCR–ABL mRNA transcripts are shown below. The first two (e13a2 and e14a2 respectively) are characteristic of CML. The bottom mRNA (e1a2) is found in the majority of patients with Ph-positive ALL (see text).

STAGING OF CML:

1. CHRONIC PHASE
2. ACCELERATED PHASE
3. BLAST PHASE

Mostly, Patients with chronic phase of CML diagnosed as an incidental finding.

Natural history of disease:

Begins typically in a chronic phase

Progress to accelerated phase after few years

Finally blast crisis

Terminal phase of CML is Blast crisis and it behaves as an acute leukemia.

Pathogenesis of progression: From chronic phase to blast crisis is abnormality of new chromosome including Ph chromosome.

CHRONIC PHASE:

At the time of diagnosis, most of the CML patients are in chronic phase which accounts 85% of the patients. Many of the patients are asymptomatic and only few have fatigue, decrease apetite, abdominal pain and joint pains. chronic phase of CML has variable duration. it also depends on early diagnosis. treatment to be started immediately after the diagnosis. if the treatment delayed then progression to accelerated phase will increase.

ACCELERATED PHASE:

Most widely used for the accelerated phase is WHO criteria

- In Bone marrow or blood :myeloblasts 10-19%
- In bone marrow or blood : basophils >20%
- Not related to therapy: Platelet count <100,000
- Cytogenetic evolution with new chromosomal abnormalities
- Not responsive to therapy: Increasing white blood cell count
- Splenomegaly.

Significance of the accelerated phase is that progression of the disease is increased where probability of transforming to blast crises increases. Effectiveness of drug therapy has reduced in the advanced stages.

BLAST CRISIS:

In blood or bone marrow:>20% lymphoblasts or myeloblasts

In bone marrow biopsy: Large clusters of blood cells presents

Presence of Chloroma

CML phase	WHO definition
Chronic stable phase	Peripheral blood blasts fewer than 10% in the blood and bone marrow
Accelerated phase	Blasts 10-19% of white blood cells in peripheral and/or nucleated bone marrow cells ; persistent thrombocytopenia (< 100 × 10^9/L) unrelated to therapy or persistent thrombocytosis (> 1000 × 10^9/L) unresponsive to therapy; increasing white blood cells and spleen size unresponsive to therapy; cytogenetic evidence of clonal evolution
Blast crisis	Peripheral blood blasts ≥ 20% of peripheral blood white blood cells or nucleated bone marrow cells; extramedullary blast proliferation; and large foci or clusters of blasts on bone marrow biopsy

CLINICAL SIGNIFICANCE

Loss of weight

Fatigue

Early satiety

Weakness

Nausea

Night sweats

Left upper quadrant pain

Fullness in abdomen

Fever

Anemia : dyspnea, palpitation, giddiness

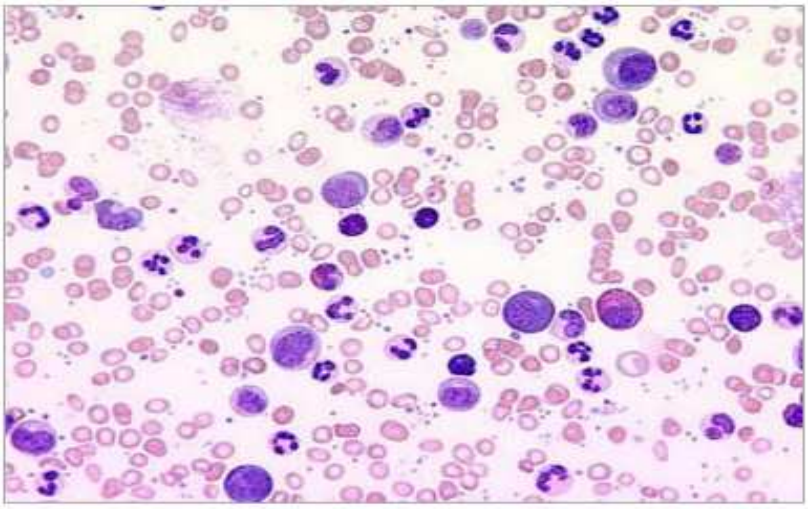
Leucopenia : infection

Thrombocytopenia : bleeding manifestation.

As a result of severe thrombosis or leucocytosis results in cerebrovascular accidents, venous thrombosis, myocardial infarction, venoocclusive disease, pulmonary insuffiency, visual disturbances. Patients have poor prognosis if associated with positive *BCR/ABL* p230.Nearly about 10 to 15% of patients have presented with accelerated phase or blast crisis. Most common finding in CML is mild to moderate splenomegaly, but Massive splenomegaly or persistent splenomegaly indicates the sign of accelerated phase. Rarely sarcoma of myeloid series and Lymphadenopathy indicate late course of the disease; the prognosis will be bad.

INVESTIGATIONS: Complete blood picture shows white blood cell counts increased with elevation of both mature and immature granulocytes. Less than 10% and less 5% circulating blasts are present along with band forms, myelocytes, metamyelocytes and promyelocytes. Platelet counts are elevated at the time of diagnosis, and Anemia of normocytic normochromic are usually present. Low alkaline phosphatase in leucocytes are present. serum uric acid levels are elevated, Serum vitamin B12 and binding proteins are increased. Basophil counts are also increased causing pruritis, flushing and diarrhea due to histamine release in later stages.[1] "*Disease acceleration* is defined by the development of Increasing degrees of anemia unaccounted for by bleeding or therapy;

cytogenetic clonal evolution; or blood or Marrow blasts between 10% and 20%, blood or marrow basophils 20% or platelet count <100,000/L."



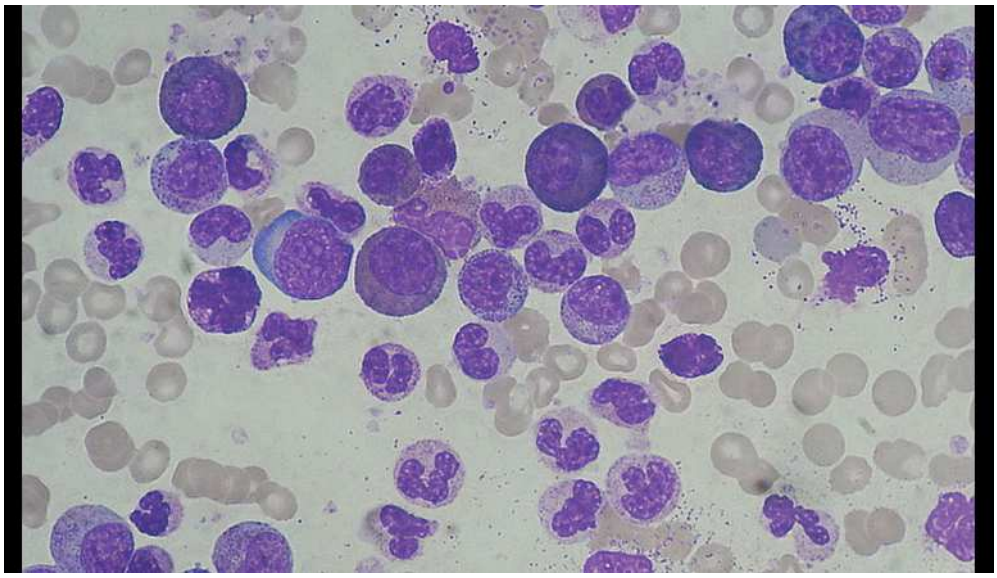
Blood film at 400X magnification demonstrates leukocytosis with the presence of precursor ce of the myeloid lineage. In addition, basophilia, eosinophilia, and thrombocytosis can be seen. Courtesy of U. Woermann, MD, Division of Instructional Media, Institute for Medical Education, University of Bern, Switzerland.

"[1]*Blast crisis* is defined as acute leukemia, with blood or marrow Blasts20%. Hypo segmented neutrophils may appear"

The hematological picture in acceleration is very variable. It may differ little from chronic phase but blast cell numbers may be increased disproportionately. There may be anemia in the presence of a normal leukocyte count. Platelet numbers may be greatly increased (1000 × 109/L) or reduced (Below 100×109/L) in a manner not accounted for treatment. The marrow also shows a picture no longer consistent with chronic-phase disease, often with increased numbers of blast cells or promyelocytes and

increased fibrosis. Blastic transformation is defined by the presence of more than30% blasts or blasts plus promyelocytes in the blood or marrow In accelerated phase of CML patients, transformation to control blood counts is poor with interferon or myelo supression. In peripheral blood smear, thrombocytopenia and basophilia not associated with therapy, presence of myelofibrosis, splenomegaly and new cytogenetic abnormalities.

Their morphologyis very variable. About 70% of patients have blasts classifiable generally as myeloid, which resemble to a degree the Cells that characterize acute myeloid leukemia. Such cells may predominantly myeloblastic, monoblastic, erythroblastic megakarocytic, and blast cells of different my eloid lineages frequently co-exist. These cells are best defined by their cytochemical and immunophenotypic characteristics.



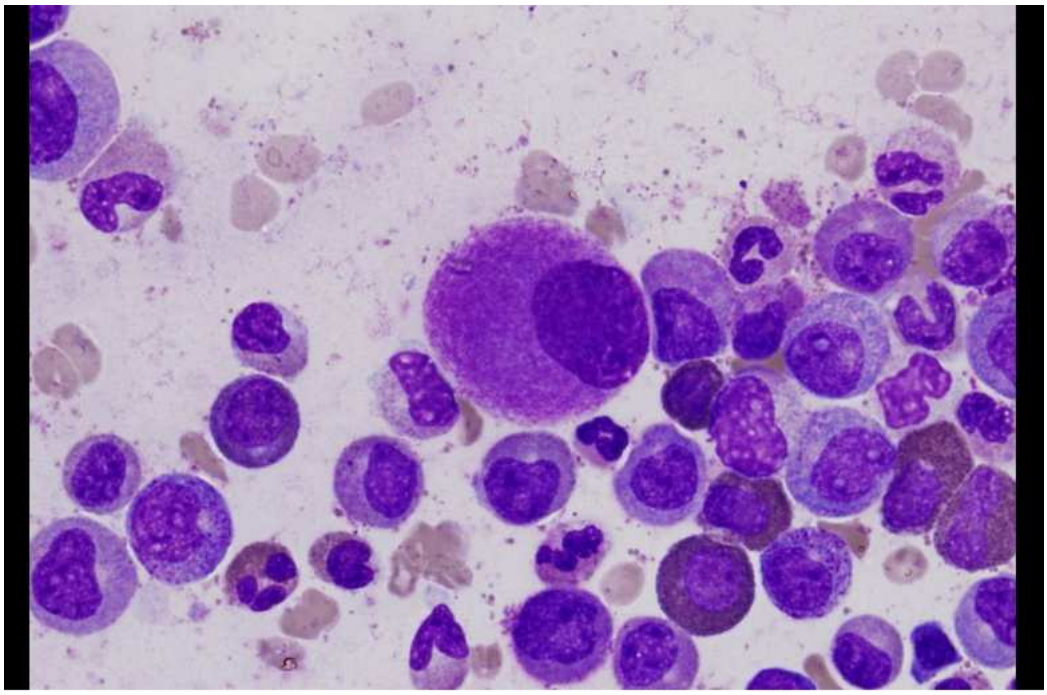
MARKED LEUCOCYTOSIS WITH GRANULOCYTE LEFT SHIFT

In CML mixed basophilic mast cell granulation as well as eosinophilia present but does not have significance for diagnosis. The picture is similar to leukemia and it should be confirmed by bone marrow biopsy.

Bone marrow examination helps to differentiate CML from reactive process and other CMPDs. Bone marrow is hypercellular, due to neutrophilic precursor proliferation to segmented neutrophils of myeloblasts. High count of Myeloblasts seen in peripheral smear and Bone marrow. In CMPDs Morphology at each stage and maturation sequence is normal. There are less than 5% of myeloblasts present in marrow. precursors are situated in periosteum normally. whereas eosinophils, hybrid cells, basophils and its precursors are present even in peripheral smear.

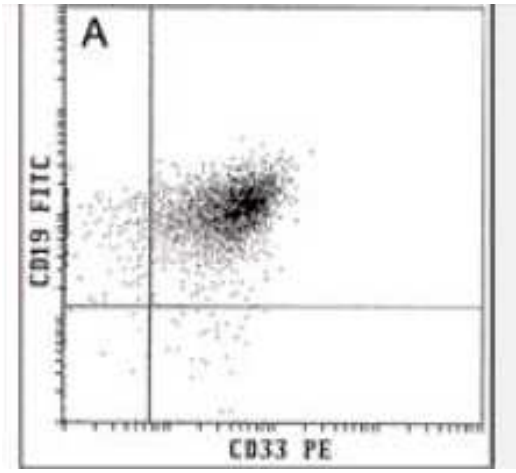
- Ph chromosome
- BCR-ABL mutation
- Hyper cellular marrow with expansion of neutrophils, eosinophils, basophils of myeloid cell line and its progenitors
- Increase in Megakaryocytes
- reticulin stain indicates mild fibrosis

Relationship between the CD61+ megakaryocyte number and its precursors with more fibrosis. Megakaryotes are increased but not as seen in essential thrombocytosis. Cluster of three or more groups are present in inter trabecular regions. Depends on number of megakaryocytes, it is divided as megakaryocytic CML where large number of megakaryotes are present. In common CML, the megakaryocytes are normal, decreased or increased. but this division have no clinical significance. About 1/3rd of patients have macrophages with Periodic acid Schiff positive, coarse, granular and cytoplasmic content like pseudo gaucher cells. These inclusions are formed from granulocyte cell membrane due to increase turn over of lipids. There are 3 types gray green birefringents, blue sea blue non birefringents, sea blue histiocytes. Staining by Prussian blue for detecting in macrophages for iron stores and it is founded that it is decreased compared with general population. Erythroid precursors in bone marrow is increased but sometimes it may decrease or normal. Anyways the ratio between myeloid to erythroid ratio is increased. By PAS or reticulin, connective tissue is not detected in marrow. Though, in myelosclerosis the fibrils of connective tissue number and thickness has been increased in marrow. Association with anemia, massive splenomegaly, increased blast cells in peripheral smear and karyotyping abnormality.

 A

SMALL HYPOLOBATED MEGAKARYOCYTE

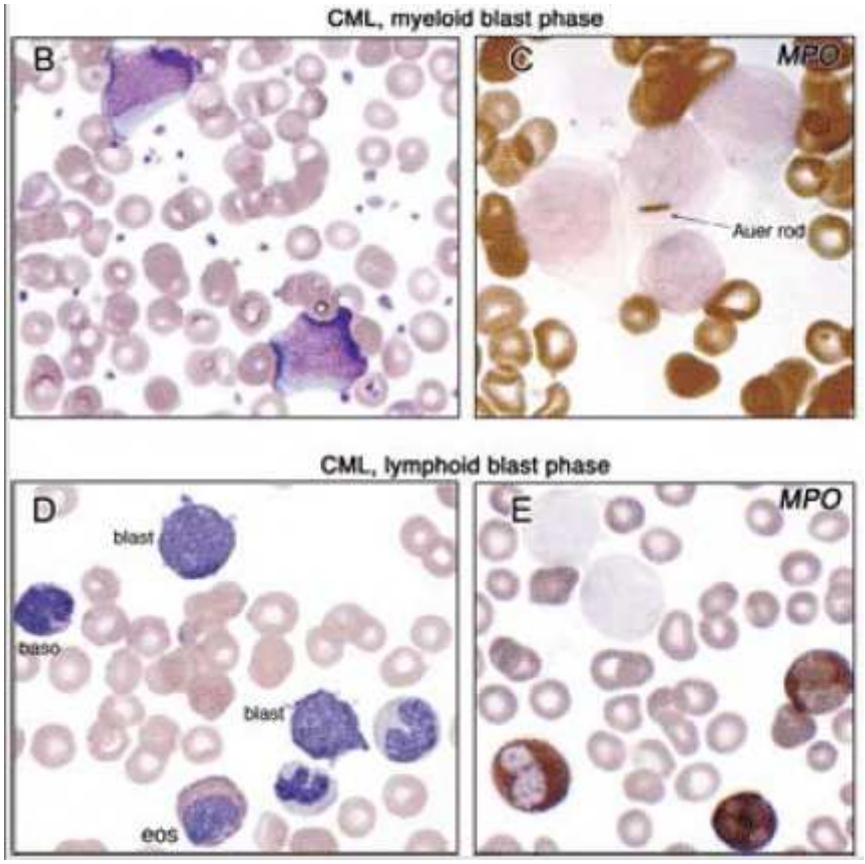
For diagnosing CML confirmation is obtained by cytogenetics by showing t(9; 22)(q3.4;q1.1)and BCR-ABL transcripts by reverse transcriptase polymerase chain reaction (RT-PCR). In Cytogenetics, through the metaphase of marrow cell, the chromosome banding analysis is confirmed. If marrow cells cannot be obtained, CBA can be substituted by interphase fluorescence in situ hybridization of blood cells, using dual color, dual fusion probes that allow the detection of BCR-ABL+ nuclei.



CBA required to detect chromosomal analysis.

FISH is required in detection of translocation variants. In peripheral blood or marrow, RNA identified by Qualitative RT-PCR. BCR-ABL protein weight (P210, rarely P230 or P190) identifies the transcript type, either e13a2 or 14a2 or very rarely e1a2, or e19a2, which accounts the BCR-ABL protein weight P210 . Real time, quantitative, PCR (RT-Q-PCR measuring BCR-ABL) will be necessary only for monitoring the response to treatment.

Definitive diagnosis and follow up depends on Ph chromosome and BCR-ABL fusion gene. Immuno histochemistry is not specific for diagnosis because it can’t distinguish CML from Leukamoid reaction. there is positive CD15,CD13 and CD33 and Myeloperoxidase expect blast crisis.

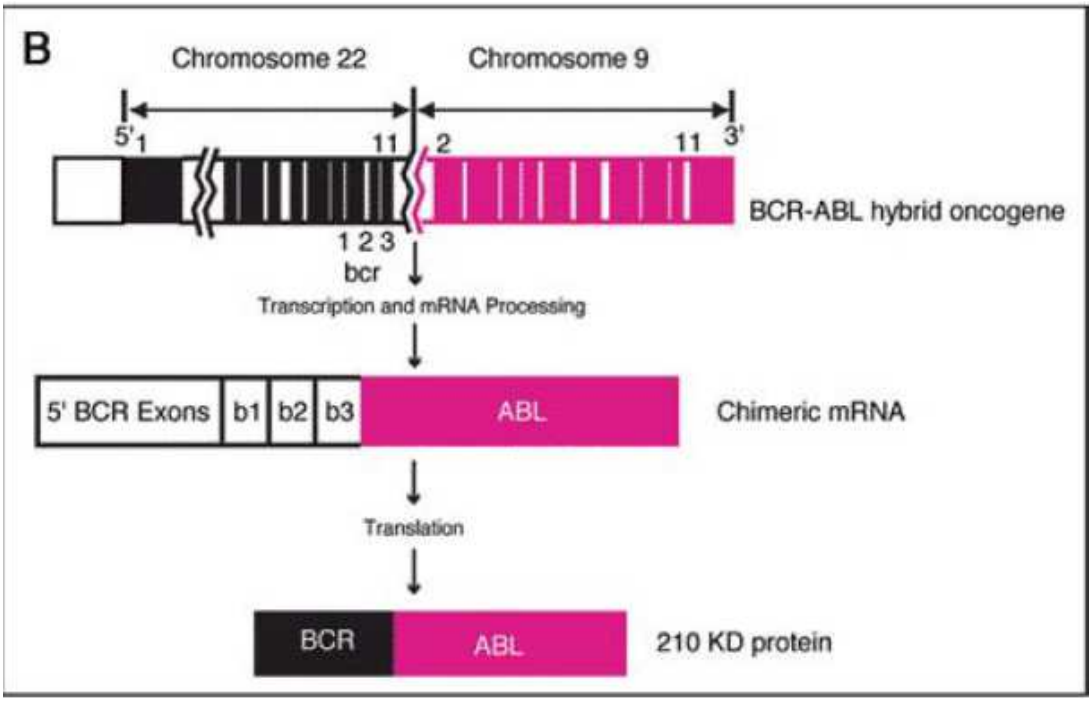


“Flow cytometric scatter gram displaying leukemic myeloid blasts co expressing both myeloid (CD33) and B-cell (CD19) markers from a case of AML complicating CML. **B** and **C.** Blood smear showing blasts and increased platelets and myeloperoxidase stain (**C**) highlight an Auer rod in one of the myeloid blasts”.

The ultimate diagnosis in CML Is FISH.

If BCR-ABL gene not identited through FISH. Then exclude the diagnosis of CML and Consider Myelodysplastic syndrome. If WBC Less than 50000 and no splenomegaly then consider leukamoid reaction. In

peripheral blood, presence of myeloblastsexclude leukamoid reaction as diagnosis. Bone marrow shows prominent Myeloid dysplasia .



Southern blot analysis Identifies rearranged BCR gene. Western blot analysis Identifies BCR-ABL gene. Fusion gene in nuclei of metaphase and interphase identified by FISH technique. Investigation of choice for intial diagnosis and it helps in diagnosing 100% in CML patients. peripheral blood and bone marrow dried smears are also identified through cryptic translocation.

The conventional karyotypingWill detect only 95% of CML patients. BCR-ABL fusion protein is formed as the results of chromosome translocation.

A.*BCR/ABL* in FISH: Philadelphia chromosome formed as the result of reciprocal translocation from *Abelson gene (ABL)* of chromosome 9 with the *breakpoint cluster region gene (BCR)* of chromosome 22.*BCR/ABL fusion gene product at molecular level.* In blood or bone marrow, FISH analysis will be performed on metaphase cells or interphase stage. At the *ABL* gene the probe is labeled with fluorophore red where as a probe at the *BCR* gene to be labeled with a "green'' fluorophore. After DNA denaturation both red and green probes are added to patient's cells and hybridization to be done. Two yellow signals are detected as the results from the *BCR-ABL* fusion gene and the presence of *BCR-ABL*, reciprocal translocation the t(9;22) (q34;q11.2) are formed. If at all,two green and two red signals are detected and ABL-BCR gene not been detected then it indicates that translocation has not been occurred and also there is no evidence of CML..**B.** sequences of BCR and ABL due to juxtaposition where as it is detected by FISH or cytogeneticsto form chimeric mRNA of size 210 kilo Dalton. The oncogenic fusion protein, BCR-ABL is transcribed by p210 and detected by RTPCR.*BCR/ABL* fusion protein Of P190 is showed by acute leukemia t(9;22), CML always

shows that the translocation of fusion product p210. Between exons b3, b4 and b2,b3 as the result, breakpoint cluster region of major Part in the *BCR* gene.

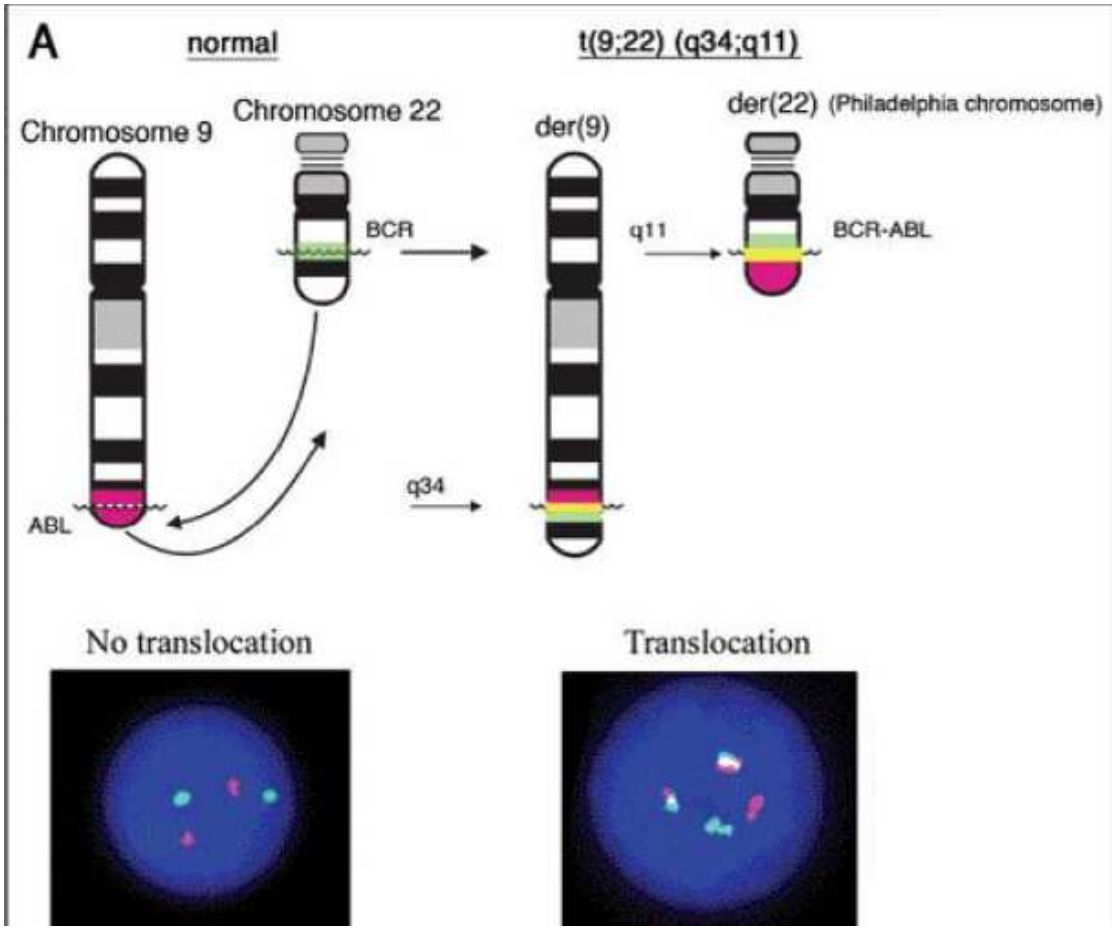
The outcome is variable in CML patients. Before treatment of the imatinib, the median survival rate is 4 years. 10% of patients expected deaths are within 2 years and every yearly 20%. Several prognostic models are developed in order to identify risk factors in CML. Stagingsystems have derived from multivariate analyses of prognostic factors.

The *Sokal index* to be predicted by splenic size, percentage of circulating blasts, platelet count, cytogenetic clonal evolution and age are the prognostic indicators. Based on chemotherapy-treatment ,these systems were identified. Based on Interferon treatment, Hansford system was developed. It is predicted through percentage of circulating blasts, spleen size, percentage of eosinophils, basophils, age and platelet count. Hansford system was better compared to the Sokal score, it helps in identifying the patients with low-risk where as in the high-risk group only a few patients have been identified. Both the hansford and the sokal systems can be used in patients with treatment under imatinib.

In CML, the therapeutic goal is durable and prolonged, nonclonal Hematopoies is, non neoplastic and the eradication the BCR/ABL transcript residual cells. Therefore the goal leads to complete cure and remission.

Tyrosine kinase inhibitors are first-line Treatment for many patients with chronic myelogenous leukemia. More than 90% Of CML patients are Philadelphia chromosome positive caused by chromosomal abnormalities. It was discovered by Janet Rowley in 1972 and therefore fusion between the Abelson tyrosine kinase gene at chromosome 9 and with the break point cluster gene at chr 22, which results in chimericoncogene and the active tyrosine kinase. bcrabl gene that has implicated in pathogenesis of CML. Multiple Compounds are developed to inhibit the tyrosine kinase selectively.

New form of resistance occurs as mis sense mutations with Abl kinase domain, Bcr-Abl over expression, increase production of plasma proteins, or activation of scrfamily kinases signaling molecules in downstream.



The Messenger RNA transcript of BCR-ABL identified by RT-PCR Qualitative technique but it is different to standardize. Hence quantitative real time PCR techniques standardization is difficult.

The conclusion reported that FISH or karyotyping is required for therapeutic purposes and guided as early phase of treatment.

Salient Features for Laboratory Diagnosis of Chronic Myelogenous Leukemia

1. Leukocytosis: 50,000 to 100,000/μL
2. Wide spectrum of myeloid cells with myelocyte bulge, basophilia, and eosinophilia in the peripheral blood
3. Hypercellular bone marrow with particular increase in myelocytes or promyelocytes, basophilia, and eosinophilia
4. Blast count: chronic phase <5%; accelerated phase 10% to 19%; blast phase >20%
5. Immunophenotype: Positive for CD13, CD15, and CD33, and increased CD34 and CD117 proportional to blast counts
6. Cell lineage of blasts should be determined by flow cytometry or immunohistochemistry.
7. Low leukocyte alkaline phosphatase (LAP) score
8. Philadelphia chromosome, t(9;22) demonstrated by karyotyping
9. Breakpoint cluster region/Ableson (BCR/ABL) gene/messenger RNA/protein detected by molecular biology techniques

The treatment for newly diagnosed CML has vastly changed in last Years. Initially, the physician used to start treatment immediately with busulphan. Information and consent about prognosis to be obtained. The various therapies are discussed at this stage, mainly for the younger patient include allogeneic SCT at some stage of the disease. The patient, families, all siblings should be genetically HLA typed. In asymptomatic patients, If the leucocytes counts below 100 × 109/L then there is no urgent to treat. This leucapheres is of bloodstem cells can be cryoprecipitated before treatment. Stored cells to be used for auto graftlater. Drug therapy should be started once diagnosis confirmed.

The best treatment at present in chronic phase for allogeneic SCT introduced as imatinib, and the number of imatinib combinations are tested and then approved. Hydroxyureais also used in the short term if imatinib is notavailable. Special indications, INF alpha and busulfan are treatment of choice alternatively.

Chronic myeloid leukemia: ESMO Clinical Practice Guidelines for diagnosis, treatment and follow-up

Table 3.
Recommendations for the diagnostic workup and for assessing and monitoring the response to treatment

	Baseline (diagnostic workup)	To assess the response	To monitor the response and the treatment
Blood counts and differential	Yes	Every 15 days until a CHR has been achieved	Every 3 months
Bone marrow, cytology	Yes	No	No
Bone marrow, Karyotype (CBA)	Yes	At 3 and 6 months, then every 6 months, until a CCgR has been achieved	Every 12 months, once a CCgR has been achieved, only if molecular response cannot be assured
Blood, I-FISH	No	No	Only if CBA of marrow cell metaphases cannot be performed, and molecular response cannot be assessed
Blood, RT-PCR (qualitative)	Yes	No	No
Blood, RT-Q-PCR (quantitative, BCR-ABL %)	No	Every 3 months until a major molecular response has been achieved	Every 6 months, once a MMR has been achieved
Mutational analysis	Only in AP or BP	No	Only in case of failure (see Table 6)

Imatinib mesylate

Imatinib mesylatealso called Glivec or Gleevec; initially known as STI571 or CGP 57148B) and it is 2-phenylaminopyrimidine compound, it is an ABL tyrosine kinase inhibitor discovered in 1998.

It originally acts by occupying ATP-binding pocket of Abl kinase which is the component of onco protein BCR–ABL, and therefore the capacity for phosphorylation of the enzyme has been blocked. Then

discovered that by binding to an domain in this manner, it can holds the Abl component of oncoprotein BCR–ABL.

The drug that rapidly reverses the hematological and clinical abnormalities and the cytogenetic responses in more than 80% of CML patients in chronic phase who were not treated. The dosage was given orally 400 mg per day, but the pilot studies, shown that the treatment with 600 mg or 800mg daily initially can give better results. Side-effects are bone pain, nausea, edema of infra orbital region, headache, rashes, and generalized fluid retention. The treatment for these side effects include interruption of imatinib temporarily from time to time. and re-instituting the corticosteroid coverage shortly for skin rashes. Hepatotoxicity detected by increasing serum SGOT and SGPT and may require to stop drug for some period of time. Recently reported that it may potentially causes cerebral oedema which may fatal. In small groups of people, reported that hair pigmentation and the interesting non-sinister effect. The toxicity of INF-alpha seems to cause comparatively less. In minority, with in few months of treatment with imatinib at standard dosage of 400 mg per day caused neutropenia andthrombocytopenia. In few cases, isolated neutropeniacan be managed with G-CSF at the dosage of 300–480 μg on alternative days subcutaneously, after which it is possible to stop or decrease the drug dosage. In other few case reports, G-CSF function is less comparatively.

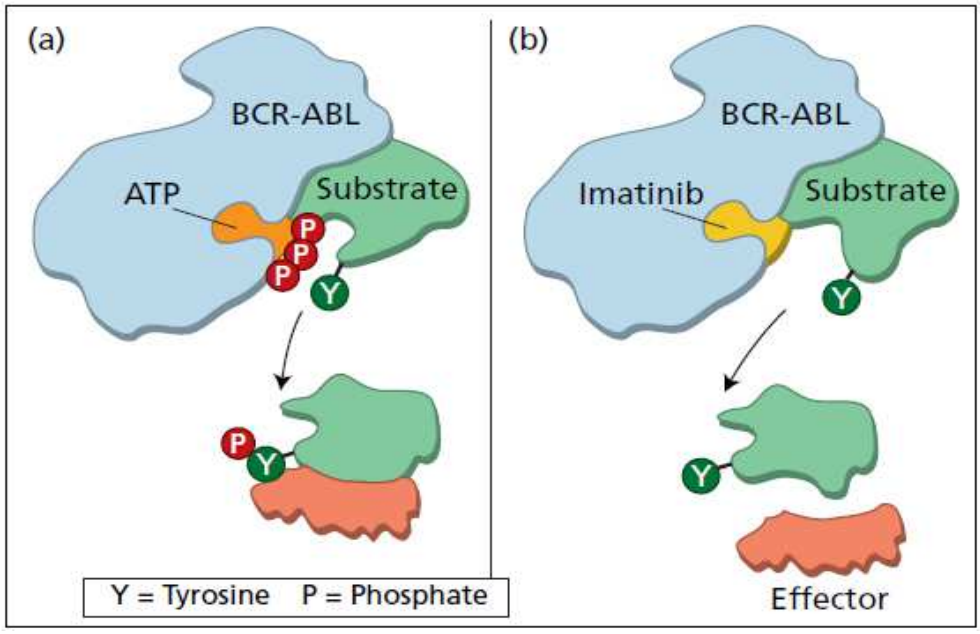
Therefore it is necessary to decrease the dose or to stop the imatinib. In case of thrombocytopenia, it is necessary to reduce the drug. daily dosage of 300mg is relatively ineffective. But thrombocytos is persisted in patients with leucocyte count which was well controlled by imatinib. In such cases, hydroxyurea oranagrelide to be added which usually controls the platelet count. But the duration of imatinib to continue is not known. For those who has attained complete cytogeneticremission, for them by stopping the drug can lead to recurrence of Ph positivity & leucocytosis in majority of cases. Although sometimes, the cytogenetic remission without treatment for many months or longer can continues. At present, the best advice to the patient is that continue the drug indefinitely. Major cytogenetic response for the patients who has failed to response after 1yr of therapy is> 66% Ph negativity in the bone marrow. Reports that, Inspite of continuing treatment with imatinib is weak and therefore other alternative approaches to be considered.

Among patients those who achieve complete cytogenetic remission, BCR–ABL transcripts are low in number. And it is usually be detected by RT-PCR, therefore conclude that eradication of CML as a single agent with imatinib is difficult.

A prospective study of phase III trial designed randomly to compare imatinib as single agent with combination of cytarabine and interferon alpha in untreated patients previously and this study started in June 2000.

The results showed, Patients with imatinib treatment about 74% of patients had a complete cytogenetic remission than to comparision with the control arm. Progression-free survival with imatinib treatment is significantly betterthan in the IFN-αand cytarabine treated patients. Statiscally proven that 97.2% versus 90.3%;hence imatinib as the single agent in causing remission is highly significant than other combination drugs reported as*P* <0.001.

Imatinib have reported that overall survival has been increased. Residual BCR–ABL transcripts and cytogenetic responses are in low levels. Proved that it is the only agent as treatment of choice for almost or all newly diagnosed CML Patients. Monitoring the response of treatment with imatinib is by FISH,bonemarrow analysis and cytogenetic studies for the *BCR–ABL* gene for patients without any cytogenetic remission.



A)‘’ATP occupies the pocket in the ABL component of the BCR–ABL oncoprotein, whence it donates a phosphate (P) group to a tyrosine (Y) residue on an unspecified substrate. The substrate then detaches itself from the BCR–ABL onco protein and makes functional contactwith a further downstream effector molecule’’

“(b) imatinib occupies the ATP binding site and thereby prevents phosphorylation of the substrate. This molecule in turn fails to make contact with the effector protein and the signal transduction pathway that would otherwise transmit the ‘leukaemia signal’ is interrupted.”

The only approach is RT-PCR for BCR–ABL transcripts to know the degree to recognize incipient relapse and response. As it indicates revised therapeutic strategy including SCT in allogenics. In patients with CML especially in chronic phase, acquisition to imatinib resistance is rare for diagnosis within the first 2 years. In patients on imatinibin ‘late chronic phase’ is more common than after treatment with other agents. Around 70% of patients those who treated during myeloid blast crisis found to have imatinib resistance and relapse is seen in all of those in lymphoid blast crisis within 6 months after initial response. Resistance is seen along with the variety of diverse mechanisms, including the point mutations acquired in the ABL kinasedomain, BCR–ABL oncoprotein, over expression and P-glycoprotein over expression, which increases the drug exit from individual cells. Thus the 20 point mutations in imatinib resistant patients

of variable degree have been identified in leukemia cells. The coding for different each amino acid substitutions in BCR–ABL oncoprotein. Cells with one substitution, replaced by an isoleucine with threonine at 315position where it is referred to as T315I mutation resistant to imatinib. Resistance is less in Cells with other substitutions. The amino acid substitutions in Abl kinase domain, one particular part where the phosphate-binding loop so called asP-loop which predicts progression of disease and also the poor survival. It is probable that these sub clones pre-exist the administration of imatinib but are allowed to expand when the wild-type molecule is inhibited by imatinib.

Hydroxyurea:

A ribonucleotide reductase inhibitor which targetsmature myeloid progenitors in the proliferative cycle. The pharmacological action is reversible and rapid. Treatmentin chronic phase starts with 1.0–2.0 g daily by oral. By treatment all the features of CML begins to reverse at the duration of 4 to 8 weeks .The size of the spleen reduces and wbc counts decreases with in few days. The hydroxyurea dose to be titrated according to the leucocyte count, therefore the maintenance dose is given between 1.0 to 1.5 g daily.

Decrease in dose of the drug causes increase in wbc counts rapidly, a phenomenon which has no ominous significance. The drug has few side-effects. At increased dosage, it causes gastrointestinal disturbance,

diarrhea, nausea, skin rashes, ulcers of the buccal mucosa. Megaloblastic changes are seen mostly in the bone marrow and macrocytosis seen in the blood. This is useful in patients who are unable to tolerate imatinib and also in newly diagnosed patients for rapid cytoreduction.

Interferon-*a*

It belongs to a member of family of glycoproteins with anti-proliferative and antiviral properties. In 1980s studies shows that human cell lines active in reducing and reversing all features of CML in about 70–80% of patients. Of particular interest, about 5–15% of patients obtained Ph-positive marrow metaphases, a major reduction with restoration of Ph-negative haemopoiesis. Founded that 'cytogenetic responders' have prolonged the life by treatment with IFN-α, and compared with hydroxyurea showed that attainment with INF-alpha is maximum cytogenetic remission according to randomized controlled studies prospectively.

These observations have proved that IFN-α has better role than busulphan and hydroxyurea in CML of chronic phase till the imatinib introduced as primary treatment. Administration of Interferon-α by subcutaneous injection ranging from 3 to 5 mega units per/m2 in daily doses. There is no evidence that the increased doses are beneficial. Toxicity is common but reversible in most of the elderly patients. Toxicity

includes muscle aches, fevers, chills and rigors and general ‘flu-like’ features by starting the drug; reduces by paracetamol but lasts for 2 to 3 weeks. When drug dosage is increased it will again recurs but few patients cannot tolerate these side effects of drugs.

But adverse effects of drugs include wt loss, alopecia, malaise, lethargy, thyrotoxicosis, depression, anorexia, lethargy. An recent introduction of pegylated IFN-α, has advantage over conventional formulations.

Busulphan:

It is an 1,4-dimethanesulphonyloxy,an alkylating agent that is not frequently used. It targets primitive stem cells and administration is prolonged after stoppage of the drug. In 1960 to 1980, it is the mainstay of treatment for CML. Conventionally treatment was started orally with 8mg daily. By using drug, wbc counts has found to be reduced. once the leukocyte count falls less than 20 × 109/L. It is the indication to reduce or stop the drug. These patients may presents with infections due to profound and prolonged leucopenia. Busulphan to be administered at a maintenance dose between 0.5 and 2.0 mg per day up to 4 weeks. Few patients were ‘hypersensitive’ to busulphan and developed irreversible, pancytopenia and marrow hypoplasia with standard dosage. Gonadal failure occurs within a few months of treatment and was almost irreversible. In elder

patients dosage of drug is 50 to 100 mg orally up to 4 weeks. Other toxicityincludes pulmonary fibrosis, cutaneous Pigmentation and hypoadrenalism.

Homoharringtonine:

Drug used in CML of chronic phase,it is ansemi synthetic plant alkaloid that causes apoptosis. In 60–70% patients, it causes hematological response and In25% of patients causes cytological responses. Improvement is seen with the addition of IFN-α. But it remains an investigational agent.

Dasatinib:

Dasatinib is second generation tyrosine kinase inhibitor which targets BCR-ABL protein .As, it was developed after the imatinib, it iscalled as *second generation* TKI. Like imatinib, it is administered orally.

Dasatinib is used as the first treatment for CML, especially in those who cannot tolerate side effects of imatinib. And it was first approved to be taken twice daily.

Adverse effects includes volume overload, diarrhea, nausea, leucopenia and cutaneous rash. More common serious effect is accumulation of fluids in the lung in form of a pleural effusion. This side effect is seen commonly seen in patients on drugs twice daily. The

accumulation of fluid is recurrent even after aspiration with needle or intercostal drainage then it is the caution for reducing the drug dosage. Indication of treatment for blast crisis, accelerated and chronic phase is that chronic myeloid leukemia with Ph positive resistance to therapy including imatinib. Start 140 mg PO qDay and may increase to 180 mg q Day if response is inadequate’’

Nilotinib

Nilotinib known as Tasigna second generation TKI which targets BCR-ABL protein. In first line therapy for CML, this drug can be used. It is indicated in patients those who are inability to tolerate the side effects of imatinib drug. Nilotinib side effectsare mild to moderate, which include gastroenteritis nausea, vomiting, diarrhea, volume overload, leucopenia. It may cause hyperglycemia and pancreatitis, but this is rare. prolonged QT interval and paroxysmal arrthymia another side effect seen. ECG before and after treatment to be mandatory. It may cause sudden cardiac death.

Bosutinib:

"Bosutinib is another TKI which targets the protein of BCR-ABL. US Food and Drug Administration has approved this drug for the treatment of patients who were already on another TKI Therapy."

Common side effects usually includes anemia, leucopenia, diarrhea, nausea, thrombocytopenia, rash, fever, abdominal pain. rarely drug can cause fluid retention, hepatotoxicity and hypersensitivity reaction.

Ponatinib

Ponatinib is a new TKI which targets the BCR-ABL protein. Reported that this drug causes serious adverse effects.Due to this, it is used rarely. T3151mutation occurs in gene where patients were treated with TKI therapy. This mutation also prevents other TKI from its action in patients with CML on treatment. Therefore in such situation, the only drug used is ponatinib. Reported that, it is the first TKI against CML cells who have T3151 mutation. Dose to be taken once daily.

Many of the side effects include abdominal pain, cutaneous rash, precoaguble states which results in Myocardial infarction, cerebrovascular accidents, DVT, hypertension, fatigue, headache, rash or other skin problems and fatigue. It is very commonly encountered in elderly patients and those with risk factors like hypertension, diabetes mellitus, and

hyperlipidemia. Other adverse effects of drug are pancreatitis,heart failure, hepatotoxicity, gastroenteritis.

Allogeneic stem cell transplantation:

In patients of young age, Allogenic stem cell transplantation is main stay of treatment with siblings of identical HLA donors. Due to major adverse effects with SCT, patients of age above 50 to 55yrs are excluded. Major factors which influences survival are duration of disease, age of onset, phase of disease at time of SCT, gender and between donor and recipient degree of histocompatibility. Immunosuppressant used in transplantation is cyclophosphamide, irradiation and combination of high dose busulphan and cyclophosphamide. After infusion of hematopoietic stem cells of donor, with in 3 to 4 weeks the function of marrowis achieved. The major complications of transplantation include venooclusive disease in liver, infection with cytomegalovirus, graft-versus-host disease, idiopathic pneumonitis. The 5yrs survival rate among HLA identical siblings, marrow transplantation is 60 to 80% of patients Among patients with transplantation, relapse rate is only 15% and mortality rate 20%. Even very low number of bcrabl is detected by RT-PCR both in bone marrow and blood. Monitoring the patients with cytogenetic studies without evidence of hematological disease. As transplantation major side effect is toxicity.

Many studies shows that graft versus leukemia had important role in eradicating the CML. New strategies shows that toxicity reduced by pre transplant precautions and immune suppressants. These focuses predominantly on the Immunosuppressive agents rather than myeloablation therapy. To increase the number of transfusion of haemopoietic stem cells, In order to reduce the GVL effects by immune competent cells of donor. Non-myeloablative, mini and reduced intensity Stem cell transplantation. In long term, NSCTs was superior by comparing conventional transplants. In Molecular methods, HLA class I and II and five gene pairs include HLA-A,HLA -B,HLA -C,HLA -DR and HLA-DQ. After transplantation allogenic SCT relapse occurs in 10 to 30%within 3years and the relapse is Insidious in nature. It is characterized by increasing transcripts levels of BCR–ABL, metaphases of Ph-positive marrow, in chronic phase of hematological features. therefore all post-transplant patients should be monitored by Cytogenetic analysis and RT-PCR. For the Treatment for relapse includes INF-gamma, imatinib, hydroxyurea and transplant for second time by using another or same donoror transfusions of lymphocytes is mainly mediating a GVL Effect through the original donor. Even though leukemia eradication is difficult. complete cytogenetic remission occurs in 3 to 6months in 80%.Graft versus host disease incidence is decreased by lymphocyte transfusion for 4 to 12 weeks it is known as escalating dose. However, imatinib is the best

treatment of choice. But in younger individuals stem cell transplant plays major role. Initial treatment should be with imatinibe for un responders an imatinib-containing combination to be used.

In antenatal patients with CML, treatment is difficult especially in first trimester it is better to delay the treatment including imatinib. When diagnosed the CML in asymptomatic patient. If needed blood transfusion and leucopharesis to be transfused. In second trimester, treatment include interferon- alpha and where as in third trimester imatinib to be given.

A fusion gene *FIP1L1-PDGFRA* in the EOL-1 cell line where nilotinib acts up on. It induces apoptosis and also it inhibits proliferation. Mechanism of action is by inhibition of the PDGFRA tyrosine kinase phospharylation. Resistance of imatinib is caused by the T674I point mutation in *FIP1L1-PDGFRA*. Modulation of the signal transduction of the tyrosine kinase results in treating diabetic retinopathy, angiogenesis, tumor growth, atherosclerosis, macular degeneration and inflammatory diseases.

The thyroid gland composed of thyroid follicular cells that secretes Thyroglobulin rich inproteinaceousfluid.Pitutary gland of anterior part Containsthyrotrope cells which secretes TSH.Thyroid axis is controlled by TSH which is used as physiologic marker of thyroid hormone.

The biologic activity of TSH hormone is influenced by Thyrotropin releasing hormone.

Hypothalamus secretes TRH

TRH stimulates pituitary gland

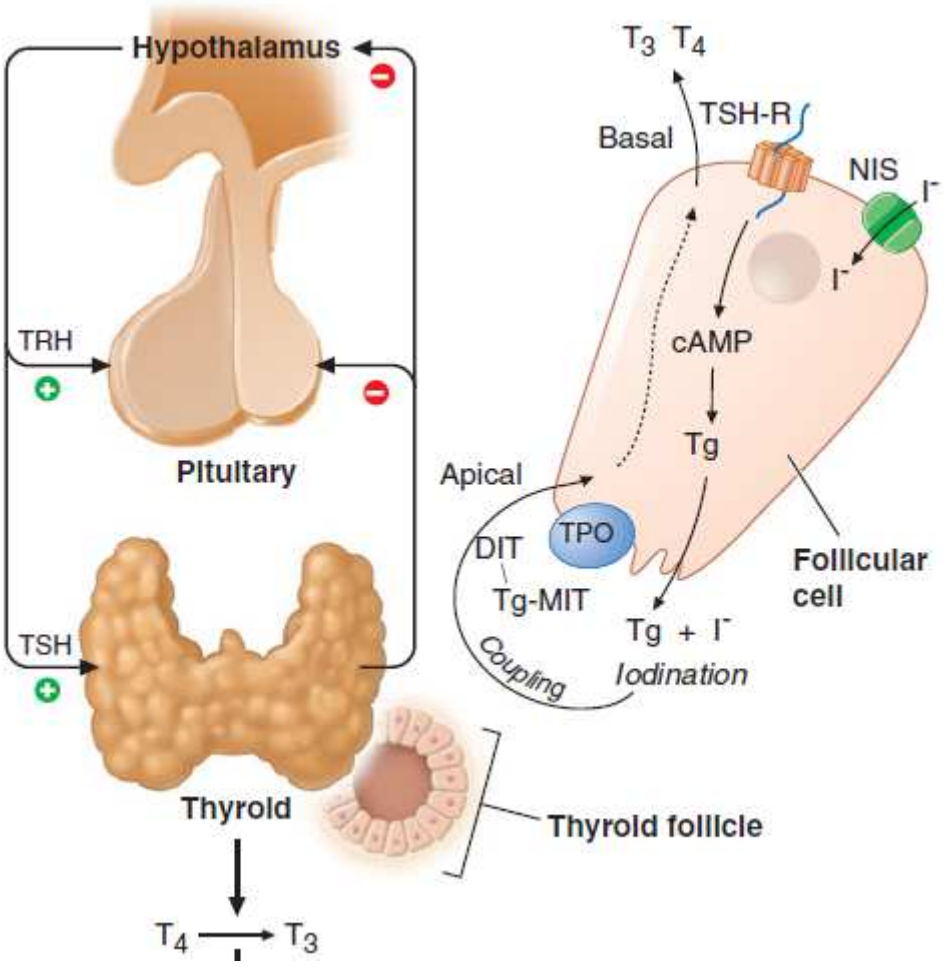
Pituitary gland secretes TSH

TSH stimulates thyroid gland

Thyroid gland secretes thyroid hormone

Feed back to inhibit TRH and TSH production

In the thyroid axis, “set point” is established by TSH. Radio immunoassays are most useful in detecting TSH levels. these are highly specific and sensitive for diagnosis of hypothyroidism and hyperthyroidism.



The thyroid gland secretes T3 and T4 by fixing and transporting amino acids in Thyroglobulin.

Depends on situations, thyroid hormones are released in the body. TRH signaling from hypothalamus results in TSH released from pituitary gland.

- Thyroid hormones in free forms are more active than bound forms.
- Mechanism of action is by entering in to the cells and binding to thyroid receptors. They alter the gene expression by transcripting the nuclear factors.

- Thyroid hormones regulates cardiac function, metabolic rate, mentation, calorigenesis and Synergistic action with catecholamines.

T3 is more potent and the precursor for T3 is T4.Conversion of T3 to T4is by the deiodinase enzymes. There are two types of deiodinase 1 and 2. Type I deiodinase, is located mainly in liver, kidney, thyroid and the affinity is low for T4.

Thyroid Hormone synthesis Thyroid hormones are derived from Thyroglobulin, a large iodinated glycoprotein. After secretion into the thyroid follicle, Thyroglobulin is iodinated on tyrosine residues that are subsequently coupled via an ether linkage. Reuptake of Thyroglobulin into the thyroid follicular cell allows proteolysis and the release of newly synthesized T4 and T3.

Iodine metabolism and transport Iodide uptake is a critical first step in thyroid hormone synthesis. Ingested iodine is bound to serum proteins, particularly albumin. Unbound iodine is excreted in the urine. The thyroid gland extracts iodine from the circulation in a highly efficient manner. For example, 10–25% of radioactive tracer (e.g., 123I) is taken up by the normal thyroid gland over 24 hours; this value can rise to 70–90% in Graves' disease. Iodide uptake is mediated by NIS, which is expressed at the basolateral membrane of thyroid follicular cells. NIS is most highly expressed in the thyroid gland, but low levels are present in the salivary

glands, lactating breast, and placenta. The iodide transport mechanism is highly regulated, allowing adaptation to variations in dietary supply. Low iodine levels increase the amount of NIS and stimulate uptake, whereas high iodine levels suppress NIS expression and uptake. The selective expression of NIS in the thyroid allows isotopic scanning, treatment of hyper thyroidism and ablation of thyroid cancer with radioisotopes of iodine, without significant effects on other organs. Mutation of the NIS gene is a rare cause of congenital hypothyroidism, underscoring its importance in thyroid hormone synthesis. Another iodine transporter, pendrin, is located on the apical surface of thyroid cells and Type II deiodinase located at thyroid gland, brain, pituitary gland, brown fat and affinity towards T4 is high. During levothyroxine replacement regulation of T3 concentration is expressed by type II deiodinase. Peripheral conversion of T4 to T3 is increased in the pituitary. Peripheral conversion is decreased in conditions like oral constrast agents, systemic diseases, chronic disease, fasting, trauma and drugs like glucocorticoids, propranolol, amiodarone and propylthiouracil. Reverse T3 is formed from inactivation of T4 andT3 By Type III deiodinase.

Tyrosine kinase inhibitors are used in the treatment of solidand haematological tumours. Tyrosine kinases takes part in oncogenesis which are inhibited by these drugs. In 2005,one case have been published that due

to use of tyrosine kinase inhibitors in CML patients there is derrangment of thyroid function test and resulted in hypothyroidism.

Based on clinical findings,numerous hypotheses proposed that TKI therapy effects the thyroid function. TKI effected the thyroid hormone metabolism and regulation which are specific for molecule. As hypothyroidism caused by therapy will halt the quality of life.

Sunitinib also inhibits tyrosine kinases receptor, which include antitumor activity, antiangiogenic and receptors of vascular endothelial growth factor. Have been reported that sunitinib causes high frequency of hypothyroidism but the mechanism is unknown.

“overt hypothyroidism with an atrophic thyroid and a marked reduction in vascularity as determined by ultrasonography, despite high levels of thyrotropin. In contrast, during the off-periods in the sunitinib treatment cycles, the volume of the thyroid recovered with an increase in vascularity despite a low level of thyrotropin. These results suggest that thyroid function and volume may depend on the vascularity, which is negatively regulated by sunitinib. Therefore it induces hypothyroidism by decreasing blood flow due to capillary regression and constriction.

Targeted therapies are newly developed drugs which inhibit the tyrosine kinases activity, known for its progression in the neoplastic therapy. Imatinib, an first line drug used in the chronic myeloid leukemia treatment and the humanized monoclonal antibody, transtuzumab against

the ERBB2 receptor tyrosine kinase, which has been used in breast cancer. It is 25% efficious. Cardiotoxicity noted as one of serious side effect which progress from left ventricular dysfunction to heart failure. Therefore it is very important to detect early features of drug adverse effects and treat accordingly. In young individuals it may cause irreversible injury to myocardium. Reported that imatinib therapy compared to nilotinib therapy, progression of disease is reduced with dose of 300mg to 400mg and blast crisis to accelerated phase. Side effects include headache and skin manifestations. Laboratory manifestations includes elevated Bilirubin levels, SGOT and SGPT but discontinuation due to these side effects are reported less. Therefore, comparision Between imatinib and nilotinib the progression, remission and side effects are beneficial with nilotinib therapy .Hence, the patients with Philadelphia chromosome positive the nilotinib is superior to imatinib.

"Nilotinib has been shown to be a more potent inhibitor of BCR-ABL than imatinib. therefore evaluated the efficacy and safety of nilotinib, as compared with imatinib"

Dasatinib, an second line agent for treatment of CML. Its induces molecular and cytogenetic responses significantly. The improvement of outcome of the patient is rapid with dastinib. The response to treatment achieved within 12 months. Dosage of drug is once daily.

The Imatinib, tyrosine kinase inhibitor, first targeted therapy for chronic-phase CML. Response of therapy and survival has good outcome.“A qualitative systematic review was conducted to qualitatively compare the clinical effectiveness, safety, and effect on quality of life of TKIs for the management of chronic, accelerated, or blast-phase CML patients”

Thyroid dysfunction in CML Ph positive patients on treatment with tyrosine kinase inhibitors:

- A new class of anticancer therapy which is multitargeted acts on receptors of growth factors are tyrosine kinase inhibitors. These are indicated in treatment for gastrointestinal stromal tumors and renal cell carcinoma. Many studies shows that TKI causes thyroid dysfunction especially produced by sunitinib maleate.

Major tyrosine kinase inhibitors	Mechanism of action
Sunitinib	Inhibition of VEGF 1–3, PDGF Ra/β, KIT, FLT3-ITD, FLT3, and Ret
Sorafenib	Inhibition of vascular endothelial growth factor receptor 2 (VEGFR 2), platelet-derived growth factor receptor (PDGFR), FLT3, Ret, and c-Kit
Imatinib	Inhibition of Bcr-Abl positive colonies from CML patients, platelet-derived growth factor (PDGF), stem cell factor (SCF), and c-Kit
Dasatinib	Inhibition of Bcr-Abl and Src family kinases (SFK)
Axitinib	Inhibition of VEGFR 1, 2, and 3 selectively
Motesanib	Inhibition of VEGFR, PDFGRs, KIT, and RET
Nilotinib	Inhibition of BCR-ABL
Pazopanib	Inhibition of VEGFR 1, 2, and 3, c-kit, and platelet-derived growth factor receptor (PDGFR)

Mechanisms of thyroid dysfunction include due to this side effect of tyrosine kinase inhibitors included are

- induction of thyroiditis
- capillary regression in the thyroid gland
- antithyroid peroxidase antibody production, and
- Iodine uptake by the thyroid gland declined.

As TKI therapy causes thyroid dysfunction, it is necessary for follow up regularly for thyroid profile and clinically for signs and symptoms of hypothyroidism. If there is derangement of thyroid function then treatment to be started for the improvement in survival and prognosis. Due to adverse effects of therapy the treatment never be discontinued. Thyroiditis as the result of drug causing hypothyroidism. Therefore monitoring of TFT is mandatory. Due to tyrosine kinase receptor abnormality in regulation causes hematological and solid tumors.

- stem-cell factor receptor - gastrointestinal stromal tumor
- platelet-derivedgrowth factor receptor-dermatofibrosarcoma
- protuberans fetal liver TK receptor 3 - acute myelogenous leukemia

Targets of TKI include domains of platelet-derived growth factor receptorα/β, mitogenactivated protein kinase/extracellular signal-regulated kinases, v-raf murine sarcoma viral oncogene homolog, RET, KIT And it inhibits the differentiation,proliferation and migration.

Recently approved by the Food and Drug Administration US, are the Sunitinib and sorafenib. These two drugs used for advanced renal cell carcinoma on the phase III trials.

Sunitinib : approved forpancreatic neuroendocrine tumorsand gastrointestinal stromal tumor.

Sorafenib : approved for hepatocellular carcinoma

Hypothyroidism Incidence after intake of sunitinib is between 53% and 85%.

Effects of sunitinib as chemotherapy used in GIST(gastrointestinal stromal tumors) had developed in 46% of patients. and transient hypothyroidism Seen in sunitinib therapy after first cycle. but by the chemotherapy ending, there is an elevation of TSH. once after starting Off phase, thyroid hormone become normal. After permanent discontinuation of therapy, the thyroid levels with in 60 days became normal. Radiological changes in form of decrease iodine uptake during ON period of therapy and return to normal in OFF period of treatment. As the number of cycles increases, thyroid dysfunction increases. Reported that median time to develop hypothyroidism is4 weeks from the intake of therapy. Few patients developed permanent hypothyroidism, out of these patients there is requirement of thyroid hormone replacement in few patients. long term use of therapy is faster to develop thyroid dysfunction compared to short term use of therapy. Sorafenib is second line oral inhibitors of tyrosine

kinase, which is approved for the treatment of renal cell carcinoma by targeting kinases like RET, BRAF, VEGFR And also used in treatment of unresectable hepatocellular carcinoma, Un differentiated thyroid cancers, lung ca, pancreaticca, prostate ca and melanoma. Incidence ranges from 20 to 36%.which is less compared to sunitib.

Imatinib, most commonly used as CML therapy. It targets tyrosine kinase approved for the treatment of GIST tumors, chronic myeloid leukemia, dermatofibrosarcoma protuberans, medullary thyroid cancer. Many studies shows that imatinib causes hypothyroidism only in those patients who are already hypothyroid. It states that thyroid dysfunction seen in patients with thyroidectomies previously,treatment for medullary thyroid carcinoma had higher incidence than compared to euthyroid patients and there is an need to increase the dose of treatment.

“Therefore reported that all patients with intact thyroid glands receiving imatinib had no thyroid dysfunction” Dasatinib, targets tyrosine kinases of second generation TKI. most commonly used in the treatment of CML Ph chromosome positive patients with resistance to imatinib. only 50% of patients developed thyroid dysfunction. only few had subclinical hypothyroidism

Tyrosine kinase inhibitors	Frequency of hypothyroidism	Frequency of isolated hyperthyroidism
Sunitinib	53–85%	10%
Sorafenib	20–36%	2.6–5%
Imatinib	90–100% (only in patients who underwent previous thyroidectomies)	0%
Motesanib diphosphate	22%	0%
Vandetanib	89%	0%
Axitinib	83–92% (small number of patients in studies included)	16%
Pazopanib	10–29%	0%
Tivozanib	5%	0%

Axitinib, approved for renal cell carcinoma which targets vascular endothelial growth factor receptors of types 1, 2, and 3.data shows thyroid dysfunction reported within one month of therapy. But many trails shows that axitinib incidence of developing hypothyroidism is more when compared to sorafenib.

Pazopanib, an second generation tyrosine kinase inhibitors approved for the treatment of renal cell carcinoma. it targets c-kit, platelet derived growth factor and VEGFR1,2,3. Incidence is less than 10% as reported. many studies after trails shows that few patients developed thyroid dysfunction in form of hypothyroidism which is common among them. Others developed subclinical hypothyroidism and other few developed hyperthyroidism.

Tivozanib inhibits the activation of VEGFR 1, 2, and 3.it is potent than other tyrosine kinase inhibitors. Incidence of developing hypothyroidism is more compared than sorefinib. This drug not only

increases TSH levels but also T3 levels. Motesanib diphosphate and vandetanib are other tyrosine kinase inhibitors used in various solid tumors also causes thyroid dysfunction. but reports shows that it is less common compared to other therapy. Mostly tyrosine kinase inhibitors causes hypothyroidism but few studies shows that hyper thyroidism also reported. Most commonly in the form of thyrotoxicosis seen with treatment of sunitinib. Sorafinib also causes thyroid autoimmunity and hyperthyroidism during the course of treatment after developing overt hypothyroidism.

One of the mechanism for thyroid dysfunction in Sunitinib was destructive thyroiditis and which was confirmed by fine needle aspiration of thyroid gland which resulted in lymphocytic thyroiditis. It was reported in 40% of patients approximately during the first cycle of chemotherapy sunitinib, causes thyroid dysfunction by inhibition of vascular endothelial growth factor receptor which are expressed by thyroid follicular cells and regulated by TSH leads to regression of capillaries. thyroid dysfunction is due to decrease blood supply to thyroid resulted in damage to thyroid gland in about 68% of patients. Thyroid damage is due to decrease of lumen and ischemic supply of blood to thyroid gland through inhibition of PDGFR. Therefore, more potent the inhibition, more the increase in thyroid dysfunction.

Bevacizumab, an well-known human monoclonal antibody targeting VEGF signaling which prevents VEGF binding to receptors,

and it is approved for non-small-cell lung cancer ,colorectal ca,renal cell ca, breast ca treatment. Though it is also acting on VEGFR but incidence of developing thyroid dysfunction is less in comparing with tyrosine kinase inhibitors. Mechanism is by decreasing vascular permeability and vasoconstriction of micro capillaries in the thyroid gland. There is an protective mechanism for lower incidence due to placenta growth factor. PIGF protects by restoring thyroid gland vascularity.

Hypothesis that sunitib inhibits iodide uptake on symporters of sodium channels. but it is reversible mechanism at the periods of OFF therapy.

Another mechanism includes development of antibodies resulting in hypothyroidism. but found in only few patients with high TSH levels. Sorafenib causing thyroid dysfunction is due to inhibition ofTSH signaling pathway, RAF pathway, PDGFR and VEGFR pathways. “Studies shows that patients developing thyroid dysfunction might tend to have their cancer better controlled through the common antiangiogenic effects affecting both the tumor and the thyroid”

Many of the tyrosine kinase inhibitors developed thyroid dysfunction during the first cycle of chemotherapy. Data is lacking whether to start thyroid replacement therapy in hypothyroidism patients or not. As per endocrine journals, thyroxine replacement to be given when TSH is above 10U/L. few data shows that there is improvement in

hypothyroid symptoms after intake of levothyroxine. Others approved that hypothyroidism is beneficial in term of survival and prognosis in patients. Thus, many studies proposed that TKI causes hypothyroidism by assuming the mechanism where few causes hyperthyroidism. Monitoring thyroid profile is mandatory during the course of treatment

Overt hypothyroidism seen in all patients who already had hypothyroidism due to thyroidectomy done previously but it is not seen in patients only on chemotherapy who did not undergo surgery. There is an increase levels of TSH in patients with therapy seen in thyroidectomy patients and the dosage of thyroxine replacement to be increased due to worsening of symptoms. Studies shows that increased TSH is due to imatinib therapy. But by discontinuing the drug, TSH levels have decreased.It indicates that the metabolism of thyroid hormone is altered by the imatinib. Most common mechanism hypothesized was iodine clearance in metabolism of thyroid hormone.

Therefore an challenge to oncologist to observe for clinical signs and symptoms of hypothyroidism and hyperthyroidism. Order for thyroid profile and treat accordingly with thyroid hormone replacement. Mandatory to do baseline thyroid function of the patients with CML on tyrosine kinase therapy before the start of the treatment, during the course of the treatment and after the therapy.

MATERIALS

AND

METHODS

MATERIAL AND METHODS

SELECTION OF VOLUNTERS:

On patients who have been confirmed to have Philadelphia chromosome positive chronic myeloid leukemicpatients, a retrospective follow up at hematology department Rajiv Gandhi government general hospital. Recommended thyroid profile to these patients before the start of imatinib treatment and monitor thyroid profile during the course of treatment after 6months of duration.

STUDY CENTRE:

Department of hematology,madras medical college and Rajiv Gandhi government general hospital, Chennai.

DURATION OF THE STUDY:

6 MONTHS

STUDY DESIGN:

Observational study

SAMPLE SIZE:

100 patients

DATA COLLECTION AND METHODS:

Blood sample taken for thyroid profile from already diagnosed CML patients in stable phase. Thyroid profile includes total T3,T4,TSH in op of hematology department.

Method used is Elisa and sensitivity is about 0.005mIu/l

Quantity : 96 tests

Range : 0.5 to 40microIu/ml

Sample volume : 50microL/well

Principal: solid phase sandwich ELISA was named by Cali biotech TSH. The anti-TSH-HRP conjugate and samples are added to the wells which are coated with Streptavidin. HRPconjugate and unbound protein washed away through washed buffer, TSH of patients sample is sandwiched between two layers of antibodies. By the addition of substrate, the color intensity is directly proportional to the TSH concentration in the samples. In relation to color intensity, the standard curve is prepared to the concentration of TSH.

STORAGE AND STABILITY:

At 2 - 8^0 C products to be stored.

Stable for 24 months.

PRODUCT/PROCEDURE/INVESTIGATION DETAILS:

Total T3,T4,TSH

INCLUSION CRITERIA: Philadelphia chromosome positive CML on tyrosine kinase inhibitors for minimum period of 6 months, Normal and abnormal thyroid Profile.

EXCLUSION CRITERIA: Philadelphia chromosome negative patients, Blast crisis.

STATISTICAL METHODS:

The statistical analysis is done based on paired t-test and p value is calculated using paired t- statistics

SPONSORSHIP:

No

CONFLIT OF INTEREST

None

OBSERVATION

AND

RESULTS

OBSERVATION AND RESULTS

STATISTICS AND ANALYSIS

1. Age in years

Age in years	Frequency	Percent
Below 30	6	6.0
31-40	13	13.0
41-50	32	32.0
51-60	28	28.0
61-70	17	17.0
Above 70	4	4.0
Total	100	100.0

In the study conducted among 100 patients, thePrevalence of thyroid dysfunction is 32% in age group of 41 to 50 yrs.

2. Sex distribution

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Male	79	79.0	79.0	79.0
	Female	21	21.0	21.0	100.0
	Total	100	100.0	100.0	

In the study conducted among 100 patients, Prevalence of thyroid dysfunction is 79% among males.

3. Thyroid Status - Before Therapy

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	91	91.0	91.0	91.0
	Hypothyroid	9	9.0	9.0	100.0
	Total	100	100.0	100.0	

In our study conducted among 100 patients,Thyroid profile before start of treatment Results shows out of 100 patients, 91% are euthyroid and 9% are hypothyroid.

4. Thyroid Status - After Therapy

		Frequency	Percent	Valid Percent	Cumulative Percent
Valid	Normal	86	86.0	86.0	86.0
	Hypothyroid	14	14.0	14.0	100.0
	Total	100	100.0	100.0	

In our study conducted among 100 patients,Thyroid profile obtained after 6months duration of therapy

Results shows out of 100 patients 14% are hypothyroid and 86% are euthyroid.

T-Test

5. Paired Samples Statistics

	Mean	Std. Deviation	P value
T3 - Before Therapy	113.35	35.355	0.074
T3 - After Therapy	108.22	34.199	

In study group, T3 before and after imatinib therapy has no statistical significance.

6. Paired Samples Test

		Paired Differences					t	df	P value
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	T3 - Before Therapy - T3 - After Therapy	5.13	9.805	.980	3.18	7.08	5.232	99	0.074

In study conducted among 100 patients,T3 before and after therapy regarding development of hypothyroidism by imatinib therapy has no statistical significance.

T-Test

7. Paired Samples Statistics

		Mean	**N**	**Std. Deviation**	**Std. Error Mean**	**P value**
Pair 1	T4 - Before Therapy	6.886	100	1.8637	.1864	
	T4 - After Therapy	6.386	100	1.9047	.1905	0.059

In our study, T4 before and after therapy has no statistical significance.

8. Paired Samples Test

		Paired Differences					t	p Value
		Mean	Std. Deviation	Std. Error Mean	e r v Lower	Upper		
Pair 1	T4 - Before Therapy - T4 - After Therapy	.500	.6988	.0699	.361	.639	7.155	0.059

In study group of 100 patients,T4 before and after therapy regarding development of hypothyroidism by imatinib therapy has no statistical significance.

T-Test

9. Paired Samples Statistics

		Mean	**N**	**Std. Deviation**	**Std. Error Mean**	**P value**
Pair 1	TSH - Before Therapy	3.616	100	1.3801	.1380	
	TSH - After Therapy	4.740	100	3.0356	.3036	0.016

In this study group, TSH before and after therapy has statistical significance, pvalue is 0.016

10. Paired Samples Test

		Paired Differences					P value	df	Sig. (2-tailed)
		Mean	Std. Deviation	Std. Error Mean	95% Confidence Interval of the Difference				
					Lower	Upper			
Pair 1	TSH - Before Therapy - TSH - After Therapy	-1.124	2.0606	.2061	-1.533	-.715	0.016	99	0.016

In study group of 100 patients, TSH before and after therapy regarding development of hypothyroidism due to imatinib therapy has statistical significance.

11.Crosstabs

Thyroid Status - Before Therapy * Thyroid Status - After Therapy Crosstabulation

Thyroid Status - Before Therapy		Thyroid Status - After Therapy		Total	P value
		Normal	Hypothyroid		
Normal	Count	86	5	91	0.056
	% within Thyroid Status - Before Therapy	94.5%	5.5%	100.0%	
	% within Thyroid Status - After Therapy	100.0%	35.7%	91.0%	
Hypothyroid	Count	0	9	9	
	% within Thyroid Status - Before Therapy	.0%	100.0%	100.0%	
	% within Thyroid Status - After Therapy	.0%	64.3%	9.0%	

Total	Count	86	14	100	
	% within Thyroid Status - Before Therapy	86.0%	14.0%	100.0%	
	% within Thyroid Status - After Therapy	100.0%	100.0%	100.0%	

Among 100 patients in the study,

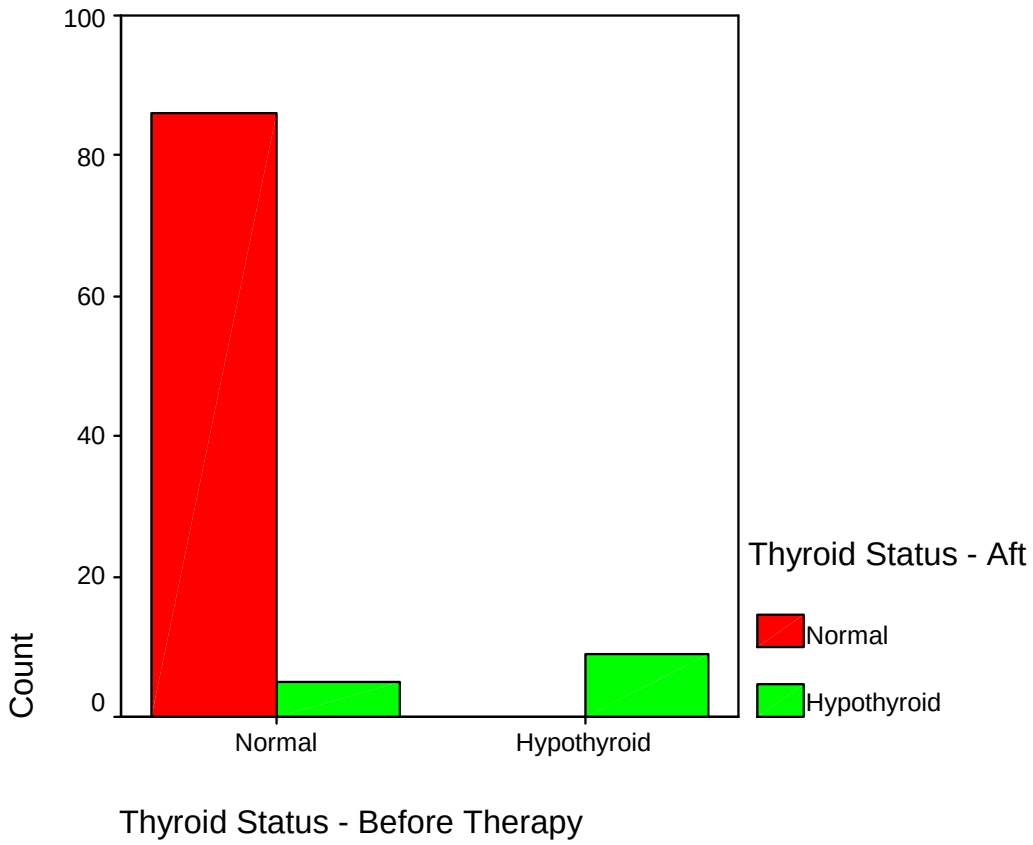
Thyroid profiles before imatinib therapy resulted in 9% hypothyroid.

Thyroid profile during the course of imatinib therapy of more than 6months duration resulted in 14% of hypothyroid.

Among 14% of hypothyroid, 5% of hypothyroid are diagnosed during therapy.

Imatinib therapy causes subclinical hypothyroid in only 5% of patients.

p value is 0.056 which has no statistical significant.



Above graph represents,majority of the patients about 86% are euthyroid after imatinib therapy.

Out of 14% of patients, 9% are already diagnosed before therapy only 5% of patients developed subclinical hypothyroid (TSH between 5 to 10, T4 & T3 - N)

Already diagnosed 9% hypothyroid patients developed overt hypothyroid. (TSH above 10, T4-I, T3-N)

12. Descriptives

Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
T3 - Before Therapy	100	49	196	113.35	35.355
T4 - Before Therapy	100	3.9	11.7	6.886	1.8637
TSH - Before Therapy	100	.9	6.9	3.616	1.3801
Valid N (listwise)	100				

Mean value of T3 before imatinib therapy-113.35

Mean value of T3 after imatinib therapy-108.22

Mean value of T4before imatinib therapy-6.88

Mean value of T4 after imatinib therapy-6.38

Mean value of TSH before imatinib therapy-3.61

Mean value of TSH after imatinib therapy-4.74

13. Descriptive Statistics

	N	Minimum	Maximum	Mean	Std. Deviation
T3 - After Therapy	100	46	185	108.22	34.199
T4 - After Therapy	100	3.1	10.9	6.386	1.9047
TSH - After Therapy	100	.9	13.8	4.740	3.0356
Valid N (listwise)	100				

In this study conducted on 100 patients, Majority have Normal T3, T4, and TSH.

Only 5% of patients have subclinical hypothyroid

9% of subclinical hypothyroid patientshave overt hypothyroid

Pvalue is 0.056 - No Statistical Significance.

DISCUSSION

DISCUSSION

An observational study was conducted at department of hematology, Madras Medical College and Rajiv Gandhi General Hospital, Chennai for a period of one year duration.

Retrospectively chosen100 Philadelphia chromosome positive CML patients on tyrosine kinase inhibitors for minimum period of 6 months were followed up at the hematology department .

Participants eligible for the study are Philadelphia chromosome positive CML patients on tyrosine kinase inhibitors for minimum period of 6months with both normal and abnormal thyroid status. From the study, participants who are excluded are CML in blast crisis and Philadelphia chromosome negative patients. Blood sample was collected to screen the Thyroid profile T3, T4,TSH in the patients before imatinib therapy and monitored during the course of therapy at minimum of 6 months duration.

Many studies have shown that tyrosine kinase inhibitors causes thyroid dysfunction in Ph chromosome positive CML patients. Our study was conducted on 100 patients to find the thyroid dysfunction in these patients.

Out of 100 patients before imatinib therapy, 9% showed subclinical hypothyroidism and 91% showed euthyroid status. After 6 months of treatment, 5% were hypothyroid out of 91% patients and 9% of Patients

with subclinical hypothyroidism had worsening of thyroid profile. It indicates that prevalence of thyroid dysfunction is minimal with imatinib therapy. Whereas patients with known subclinical hypothyroidism has increased thyroid dysfunction after the imatinib therapy. Thus there is a need to increase the dose of thyroxine in these hypothyroid patients.

Thus imatinib has effect on thyroid function or its metabolism because the TSH values is statistically increased in subclinical hypothyroid patients after imatinib therapy.

One study by Groot et al. reported that : Imatinib therapy does not cause thyroid dysfunction in euthyroid patients whereas already hypothyroid patients (included in this study with medullary thyroid carcinoma and thyroidectomised patients) had significant increase in TSH levels. As a result the need for levothyroxine dose to be increased in these patient as imatinib causes enzyme induction by clearance of nondeiodination.

Our study has a larger study population than the above study. They have monitored TFT only for 16 weeks of duration. But in our study we have included only imatinib among tyrosine kinase inhibitors due to only availability of the drug whereas in the above study all generations of tyrosine kinase inhibitors were used.

Abraham etal.reported : that thyroid abnormalities in form of sub clinical hypothyroidism is more prevalent in women with CML in south India.

Foldeset el., stated: that CML itself does not have any effect on thyroid function to results in hypothyroidism.

In another study by Jose' Miguel Dora reported: that imatinib does not causes thyroid dysfunction in euthyroid patients. In this study conducted on 70 patients, the T3,T4, TSH were within the normal levels and already known hypothyroid patients were excluded. The mechanism of hypothyroidism was found to be that "imatinib induces conjugation of giucoronates and sulfates in liver". TSH before therapy and sample size are limitation in this study. This study concluded that imatinib has no effect on thyroid dysfunction in euthyroid patients.

Multiple studies reported that, other tyrosine kinase inhibitors like sunitib, sorafenib, dastinib, pozatinib, nilotinib. sunitib are very potent to cause hypothyroidism within few weeks of therapy. About 85% of cases have been effected.

In our study, only 5% of euthyroid patients had subclinical hypothyroidism after imatinib therapy more than 6months of duration. Whereas 9% of subclinical hypothyroid patients developed overt hypothyroidism after imatinib therapy. Rest 86%of patients remained

euthyroid after imatinib therapy for more than 6months duration of therapy. This study indicates that imatinib does not cause statistically significant thyroid dysfunction in euthyroid CML Ph chromosome positive patients.

Imatinib has minimal effects on peripheral metabolism of thyroid hormones causing the development of overt hypothyroidism in patients with subclinical hypothyroidism. Prevalence of hypothyroidism in imatinib treated CML Ph chromosome positive patients has statistical insignificance. Thus imatinib therapy is not associated with the development of hypothyroidism more than general population.

CONCLUSION

CONCLUSION

Although the incidence of hypothyroidism in our study population was insignificant the presence of statistically significant TSH increase makes it mandatory to screen thyroid profile in CML patients before the start of tyrosine kinase inhibitors .Monitor thyroid profile during the course of treatment and after the therapy, to look for thyroid dysfunction. In subclinical hypothyroid patients, strict regular follow up is recommended .Early diagnosis and treatment will improve the quality of life, survival and prognosis.

Discontinuation of imatinib therapy due to hypothyroidism is not encouraged.

FUTURE SCOPE

Many studies to be encouraged to know thyroid dysfunction due to tyrosine kinase inhibitors. Studies related to duration, dosage of thyroid hormone replacement to be reported for the better quality of life in stable CML patients. In future, more studies are needed to support our findings.

LIMITATIONS

LIMITATIONS

Small sample size, duration of study, no comparisons with other generations of tyrosine kinase inhibitors, relationship of thyroid dysfunction with duration and dosage of therapy, anti-thyroid antibodies .

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ANNEXURES

ABBREVIATIONS

CML	:	chronic myeloid leukemia
Ph	:	Philadelphia chromosome
BCR	:	Breakpoint cluster region gene
ABL	:	Abelson gene
STAT	:	Signal transducers and activators of transcription.
PI3-K	:	Phosphatidylinositol 3-kinase
GM-CSF	:	Granulocyte macrophage colony stimulating factor.
SCT	:	Stem cell transplant
FISH	:	fluorescence insitu Hybridization
RT-Q PCR	:	real time quantitative PCR
VEGFR	:	vascular endothelial growth factor receptors
CMPD	:	chronic myeloproliferative disease.
GRB-2	:	growth factor receptor bound protein.
TKI	:	Tyrosine kinase inhibitors
CBA	:	chromosome banding analysis

PROFORMA

NAME OF THE PATIENT :

AGE / SEX :

IP/OP NUMBER :

OCCUPATION :

ADDRESS :

CONTACT NUMBER :

COMPLAINTS :

PAST HISTORY :

TREATMENT HISTORY :

DRUG ALLERGY :

GENERAL EXAMINATION :

VITALS :

SYSTEMIC EXAMINATION

CARDIOVASCULAR SYSTEM:

RESPIRATORY SYSTEM :

ABDOMEN :

CENTRAL NERVOUS SYSTEM

THYROID PROFILE:

LIVER FUNCTION TESTS:

ULTRASOUND ABDOMEN:

ULTRASOUND NECK:

COAGULATION PROFILE:

DATE OF STARTING THYROID PROFILE:

DATE OF ENDING THYROID PROFILE :

TOTAL DURATION :

COMPLIANCE :

SIDE EFFECTS

INFORMATION SHEET

We are conducting a study on "THYROID DYSFUNCTION CAUSED BY TYROSINE KINASE INHIBITORS IN PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA" among patients attending Rajiv Gandhi Government General Hospital, Chennai and for that your specimen may be valuable to us.

The purpose of this study is to ASSESS "THYROID DYSFUNCTION IN PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKAMIA PATIENTS."

We are selecting certain cases and if you are found eligible, we may be using your specimen to perform extra tests and special studies which in any way do not affect your final report or management.

The privacy of the patients in the research will be maintained throughout the study. In the event of any publication or presentation resulting from the research, no personally identifiable information will be shared.

Taking part in this study is voluntary. You are free to decide whether to participate in this study or to withdraw at any time; your decision will not result in any loss of benefits to which you are otherwise entitled.

The results of the special study may be intimated to you at the end of the study period or during the study if anything is found abnormal which may aid in the management or treatment.

Signature of Investigator | Signature of Participant

Date :

Place :

ஆராய்ச்சி தகவல் தாள்

இரத்தப்புற்றுநோய் (Philadelphia Chromosome Positive CML) உள்ள நோயாளிகளின் Tyrosine Kinase Inhibitors எடுத்து வருபவர்களிடம் ஏற்படும் தைராய்டு வியாதிகளை பற்றி அறியும் ஆராய்ச்சி

நீங்களும் இந்த ஆராய்ச்சியில் பங்கேற்க நாங்கள் விரும்புகிறோம். இந்த ஆராய்ச்சியில் உங்களுடைய திசுக்களை எடுத்து சில சிறப்பு பரிசோதனைக்கு உட்படுத்தி அதன் தகவல்களை ஆராய்வோம். அதனால் தங்களது நோயின் ஆய்வறிக்கையோ அல்லது சிகிச்சையோ பாதிப்பு ஏற்படாது என்பதையும் தெரிவித்துக்கொள்கிறோம்.

முடிவுகளை அல்லது கருத்துக்களை வெளியிடும்போதோ அல்லது ஆராய்ச்சியின்போதோ தங்களது பெயரையோ அல்லது அடையாளங்களையோ வெளியிட மாட்டோம் என்பதை தெரிவித்துக்கொள்கிறோம்.

இந்த ஆராய்ச்சியில் பங்கேற்பது தங்களுடைய விருப்பத்தின்பேரில்தான் இருக்கிறது. மேலும் நீங்கள் எந்த நேரமும் இந்த ஆராய்ச்சியிலிருந்து பின்வாங்கலாம் என்பதையும் தெரிவித்துக்கொள்கிறோம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

PATIENT CONSENT FORM

Study Detail	:	"THYROID DYSFUNCTION CAUSED BY TYROSINE KINASE INHIBITORS IN PHILADELPHIA CHROMOSOME POSITIVE CHRONIC MYELOID LEUKEMIA"
Study Centre	:	Department of HEMATOLOGY, Rajiv Gandhi Government General Hospital, Chennai.
Patient's Name	:	
Patient's Age	:	
Identification Number	:	

Patient may check (☑) these boxes

I confirm that I have understood the purpose of procedure for the above study. I have the opportunity to ask question and all my questions and doubts have been answered to my complete satisfaction. ☐

I understand that my participation in the study is voluntary and that I am free to withdraw at any time without giving reason, without my legal rights being affected. ☐

I understand that sponsor of the clinical study, others working on the sponsor's behalf, the ethical committee and the regulatory authorities will not need my permission to look at my health records, both in respect of current study and any further research that may be conducted in relation to it, even if I withdraw from the study I agree to this access. However, I understand that my identity will not be revealed in any information released to third parties or published, unless as required under the law. I agree not to restrict the use of any data or results that arise from this study. ☐

I agree to take part in the above study and to comply with the instructions given during the study and faithfully cooperate with the study team and to immediately inform the study staff if I suffer from any deterioration in my health or well being or any unexpected or unusual symptoms. ☐

I hereby consent to participate in this study. ☐

I hereby give permission to undergo complete clinical examination , biochemical, immunological test. ☐

Signature of Investigator

Study Investigator's Name:

Dr.M.AMARAVATHI.

Signature/thumb impression

Patient's Name and Address:

ஆராய்ச்சி ஒப்புதல் கடிதம்

ஆராய்ச்சி தலைப்பு

இரத்தப்புற்றுநோய் (Philadelphia Chromosome Positive CML) உள்ள நோயாளிகளின் Tyrosine Kinase Inhibitors எடுத்து வருபவர்களிடம் ஏற்படும் தைராய்டு வியாதிகளை பற்றி அறியும் ஆராய்ச்சி

இந்த ஆராய்ச்சியில் உங்களிடமிருந்து 10 மி.லி இரத்தம் எடுக்கப்படும். Thyroid Function Test எடுக்கப்படும். தேவையெனில் தைராய்டு சதை பரிசோதனை, USG Neck பரிசோதனை செய்யப்படும்.

இந்த ஆராய்ச்சின் விவரங்களும் அதன் நோக்கங்களும் முழுமையாக எனக்கு தெளிவாக விளக்கப்பட்டது.

எனக்கு விளக்கப்பட்ட விஷயங்களை நான் புரிந்துகொண்டு எனது சம்மதத்தை தெரிவிக்கிறேன்.

இந்த ஆராய்ச்சியில் பிறரின் நிர்பந்தமின்றி என் சொந்த விருப்பத்தின்பேரில் பங்கு பெறுகின்றேன். இந்த ஆராய்ச்சியில் இருந்து நான் எந்நேரமும் பின்வாங்கலாம் என்பதையும் அதனால் எந்த பாதிப்பும் ஏற்படாது என்பதையும் நான் புரிந்துகொண்டேன்.

நான் என்னுடைய சுய நினைவுடனும் மற்றும் முழு சுதந்திரத்துடனும் இந்த மருத்துவ ஆராய்ச்சியில் என்னை சேர்த்துக்கொள்ள சம்மதம்.

ஆராய்ச்சியாளர் கையொப்பம் **பங்கேற்பாளர் கையொப்பம்**

நாள் :
இடம் :

INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE, CHENNAI-3

EC Reg No.ECR/270/Inst./TN/2013
Telephone No. 044 25305301
Fax : 044 25363970

CERTIFICATE OF APPROVAL

To
Dr.M.Amaravathi
Postgraduate in M.D.(General Medicine)
Madras Medical College
Chennai – 600 003.

Dear Dr. M.Amaravathi,

The Institutional Ethics Committee has considered your request and approved your study titled **"Thyroid Dysfunction Caused by Tyrosine Kinase Inhibitors in Philadelphia Chromosome Positive Chronic Myeloid Leukemia" No.30102014.**

The following members of Ethics Committee were present in the meeting held on 07.10.2014 conducted at Madras Medical College, Chennai-3.

1. Dr.C.Rajendran, M.D.,	: Chairperson
2. Dr.R.Vimala, M.D., Dean, MMC, Ch-3	: Deputy Chairperson
3. Prof.B.Kalaiselvi, M.D., Vice-Principal, MMC, Ch-3	: Member Secretary
4. Prof.R.Nandini, M.D., Inst.of Pharmacology, MMC	: Member
5. Prof.P.Ragumani, M.S., Professor, Inst.of Surgery, MMC	: Member
6. Prof.Md.Ali, M.D., D.M., Prof. & HOD of Medl.G.E., MMC	: Member
7. Prof.K.Ramadevi, Director , Inst.of Biochemistry, MMC	: Member
8. Prof.Saraswathy, M.D., Director, Pathology, MMC, Ch-3	: Member
9. Prof.S.G.Sivachidambaram, M.D., Director i/c, Inst.of Internal Medicine, MMC	: Member
10. Thiru S.Rameshkumar, Administrative Officer	: Lay Person
11. Thiru S.Govindasamy, B.A., B.L.,	: Lawyer
12. Tmt.Arnold Saulina, M.A., MSW.,	: Social Scientist

We approve the proposal to be conducted in its presented form.

The Institutional Ethics Committee expects to be informed about the progress of the study and SAE occurring in the course of the study, any changes in the protocol and patients information/informed consent and asks to be provided a copy of the final report.

22/1/15

Member Secretary, Ethics Committee
MEMBER SECRETARY
INSTITUTIONAL ETHICS COMMITTEE
MADRAS MEDICAL COLLEGE
CHENNAI-600 003

MASTER CHART

S.NO	AGE/SEX	BEFORE IMATINIB THERAP PRETREATMENT					DURATION OF IMATINIB THERAPY		AFTER IMATINIB THERAPY POST TREATMENT				
		T3 (60-200)	T4 (4.5-12)	TSH (0.30-5.5)		THYROID STATUS			T3 (60-200)	T4 (4.5-12)	TSH (0.30-5.5)		THYROID STATUS
1	56/M	117	8.2	3.2		NORMAL	11MONTHS		122	7.8	3.7		NORMAL
2	49/M	89	6.4	2.8		NORMAL	9 MONTHS		87	5.9	3		NORMAL
3	52/F	76	5.8	1.3		NORMAL	11MONTHS		78	5.4	1.5		NORMAL
4	42/M	123	7.8	4.1		NORMAL	24MONTHS		125	7.6	4.6		NORMAL
5	59/M	189	9.6	4.6		NORMAL	19 MONTHS		176	9.1	5		NORMAL
6	47/M	93	5.9	3.9		NORMAL	8MONTHS		94	5.4	3.2		NORMAL
7	32/F	104	7.2	2.8		NORMAL	11 MONTHS		98	7.1	2.7		NORMAL
8	43/M	70	10.3	4.5		NORMAL	23 MONTHS		52	8.9	7.1		HYPOTHYROID
9	65/M	154	6.1	1.3		NORMAL	7M0NTHS		143	5.1	1.9		NORMAL
10	34/M	167	5.8	2.8		NORMAL	8MONTHS		170	5.9	2.8		NORMAL
11	43/F	79	4.9	0.9		NORMAL	9MONTHS		81	4.7	1.2		NORMAL
12	65/M	156	5.9	2.9		NORMAL	15MONTHS		160	6.1	3.2		NORMAL
13	52/M	76	4.6	1.1		NORMAL	28MONTHS		82	4.9	1.8		NORMAL
14	41/M	178	9	4.9		NORMAL	9MONTHS		181	10.6	5.2		NORMAL
15	65/F	98	6.6	1.9		NORMAL	9MONTHS		109	6.9	2.9		NORMAL
16	59/F	161	8.3	4.8		NORMAL	21MONTHS		168	10.6	5.9		NORMAL
17	39/M	92	6.1	4.9		NORMAL	13MONTHS		98	5.3	4.8		NORMAL
18	61/M	183	11.2	5.1		NORMAL	11MONTHS		179	10.9	5.3		NORMAL
19	29/M	121	7.1	3.9		NORMAL	21MONTHS		119	6.2	3.3		NORMAL
20	72/M	116	4.8	1.6		NORMAL	9MONTHS		98	4.5	0.9		NORMAL
21	57/M	72	4.8	4.1		NORMAL	18MONTHS		46	3.6	7.9		HYPOTHYROID
22	49/M	48	4.5	6.1		HYPOTHYROID	27MONTHS		34	4.1	12.9		HYPOTHYROID
23	45/F	87	8.1	4.6		NORMAL	7M0NTHS		82	7.5	3.9		NORMAL
24	52/F	67	4.7	1.9		NORMAL	12MONTHS		71	5.1	2.6		NORMAL
25	36/M	87	5.7	2.3		NORMAL	13MONTHS		84	4.9	2.9		NORMAL
26	42/M	113	8.4	1.4		NORMAL	10MONTHS		109	6.9	2.3		NORMAL
27	65/M	147	7.3	3.1		NORMAL	8MONTHS		137	6.9	2.5		NORMAL
28	50/M	196	9.6	4.3		NORMAL	7MONTHS		173	8.7	3.9		NORMAL
29	40/M	123	7.9	3.2		NORMAL	10MONTHS		119	7.1	2.9		NORMAL
30	53/M	109	5.3	2.9		NORMAL	14MONTHS		102	5.1	1.9		NORMAL
31	49/M	154	10.6	4.2		NORMAL	21MONTHS		160	9.8	4.7		NORMAL
32	52/F	78	6.1	2.3		NORMAL	9MONTHS		81	6.6	2.8		NORMAL

33	57/M	89	5.9	2.7		NORMAL	11MONTHS		93	5.1	2.1		NORMAL
34	46/M	92	8.1	3.1		NORMAL	15MONTHS		89	7.8	2.9		NORMAL
35	39/F	72	5.1	1.1		NORMAL	16M0NTHS		69	4.9	1.2		NORMAL
36	41/M	110	9.8	1.4		NORMAL	9MONTHS		110	8.9	1.2		NORMAL
37	39/M	161	11.7	4.1		NORMAL	16M0NTHS		121	10.3	3.9		NORMAL
38	47/M	112	7.8	2.9		NORMAL	15MONTHS		110	7.2	2.1		NORMAL
39	43/M	92	6.8	3.3		NORMAL	12MONTHS		85	6.1	2.5		NORMAL
40	52/M	121	8.9	3.9		NORMAL	13MONTHS		91	5.9	4.1		NORMAL
41	49/M	161	8.6	4.1		NORMAL	11MONTHS		154	8.1	4.7		NORMAL
42	54/M	98	7.9	3.6		NORMAL	24MONTHS		78	6.5	8.3		HYPOTHYROID
43	29/M	87	10.1	3.3		NORMAL	9MONTHS		81	9.4	5.1		NORMAL
44	67/M	172	8.9	4.6		NORMAL	13MONTHS		161	8.5	5.1		NORMAL
45	50/M	142	6.9	3.7		NORMAL	7MONTHS		136	6.1	4.1		NORMAL
46	28/M	93	6.1	4.1		NORMAL	1OMONTHS		89	5.6	4.7		NORMAL
47	30/F	84	8.7	3.9		NORMAL	12MONTHS		79	7.4	4.9		NORMAL
48	51/M	156	9.3	4.9		NORMAL	21MONTHS		143	8.4	5.1		NORMAL
49	67/F	119	6.9	3.7		NORMAL	20MONTHS		112	5.9	4.2		NORMAL
50	49/M	150	9.4	2.2		NORMAL	11MONTHS		143	8.9	3.8		NORMAL
51	37/M	71	4.7	5.6		HYPOTHYROID	21MONTHS		42	3.6	13.7		HYPOTHYROID
52	52/F	128	5.9	4.1		NORMAL	10MONTHS		116	5.6	4.6		NORMAL
53	41/M	171	7.3	3.4		NORMAL	28MONTHS		163	6.9	4.1		NORMAL
54	67/M	121	5.8	2.8		NORMAL	13MONTHS		119	4.9	3.9		NORMAL
55	56/M	146	7.2	3.8		NORMAL	21MONTHS		132	7.8	3.9		NORMAL
56	43/M	121	6	3.1		NORMAL	12MONTHS		112	6.3	3.7		NORMAL
57	51/F	137	8.4	3.9		NORMAL	11MONTHS		121	7.2	3.1		NORMAL
58	62/F	141	7.3	3.1		NORMAL	8MONTHS		118	6.9	2.9		NORMAL
59	54/M	79	5.2	4.7		NORMAL	23MONTHS		76	5.1	5.2		NORMAL
60	68/M	92	7.2	4.9		NORMAL	19MONTHS		85	6.2	5.1		NORMAL
61	42/M	56	4.5	6.9		HYPOTHYROID	36MONTHS		42	3.9	13.6		HYPOTHYROID
62	76/M	78	5.9	4.6		NORMAL	41MONTHS		82	6.3	4.1		NORMAL
63	55/M	88	5.9	3.9		NORMAL	11MONTHS		91	6.1	4.8		NORMAL
64	44/M	78	5.8	1.1		NORMAL	9MONTHS		72	5.1	1.9		NORMAL
65	52/M	118	6.2	4.9		NORMAL	10M0NTHS		89	5.1	8.3		HYPOTHYROID
66	39/M	161	8.3	5.1		NORMAL	8MONTHS		165	8.1	5.1		NORMAL
67	40/M	123	6.5	2.8		NORMAL	15MONTHS		119	6.1	3.1		NORMAL
68	69/M	92	4.9	1.6		NORMAL	9MONTHS		89	4.2	3.1		NORMAL

69	49/M	87	5.9	2.1		NORMAL	18MONTHS		82	4.7	3.1		NORMAL
70	72/M	167	10.9	3.3		NORMAL	12MONTHS		148	9.2	7.2		HYPOTHYROID
71	49/F	101	4.9	2.3		NORMAL	7MONTHS		98	4.2	3.3		NORMAL
72	61/M	92	5.6	2.1		NORMAL	16M0NTHS		85	6.1	4.1		NORMAL
73	55/M	111	4.4	2.7		NORMAL	18MONTHS		110	4.2	3.1		NORMAL
74	33/F	99	5.9	4.2		NORMAL	21MONTHS		95	5.5	5.1		NORMAL
75	41/F	63	4.2	5.9		HYPOTHYROID	9MONTHS		51	3.3	9.3		HYPOTHYROID
76	63/M	143	7.9	3.8		NORMAL	13MONTHS		136	7.2	4.1		NORMAL
77	39/M	156	8.4	4.1		NORMAL	22MONTHS		145	7.9	4.5		NORMAL
78	45/M	54	3.9	6.2		HYPOTHYROID	29MONTHS		42	3.7	10.7		HYPOTHYROID
79	62/M	99	6.7	3.5		NORMAL	12MONTHS		92	6.2	4.5		NORMAL
80	76/M	68	7.8	4.4		NORMAL	32MONTHS		71	7.3	4.5		NORMAL
81	36/F	49	3.9	6.9		HYPOTHYROID	18MONTHS		41	3.2	11.3		HYPOTHYROID
82	52/M	118	6.4	4.3		NORMAL	23MONTHS		121	6.4	4.8		NORMAL
83	48/M	131	5.9	3.8		NORMAL	16M0NTHS		129	5.4	4.9		NORMAL
84	51/M	121	8.9	4.1		NORMAL	10M0NTHS		111	8.2	4.9		NORMAL
85	64/M	190	7.9	3.9		NORMAL	19MONTHS		185	7.1	4.1		NORMAL
86	42/M	55	3.9	5.5		HYPOTHYROID	18MONTHS		48	3.2	11.4		HYPOTHYROID
87	29/F	78	4.8	4.2		NORMAL	8M0NTHS		76	5.1	5.1		NORMAL
88	54/M	102	4.9	3.5		NORMAL	12MONTHS		111	4.2	4.2		NORMAL
89	46/F	48	3.9	5.8		HYPOTHYROID	22MONTHS		39	3.7	12.8		HYPOTHYROID
90	61/M	87	7.5	4.1		NORMAL	7MONTHS		89	7.2	4.8		NORMAL
91	44/M	156	10.3	3.7		NORMAL	12MONTHS		129	10.1	4.9		NORMAL
92	51/M	132	7.5	3.2		NORMAL	9MONTHS		128	7.6	3.8		NORMAL
93	49/M	176	11.6	1.1		NORMAL	6MONTHS		165	10.9	1.9		NORMAL
94	58/M	113	6.8	1.8		NORMAL	11MONTHS		110	6.4	2.4		NORMAL
95	59/M	109	5.9	2.1		NORMAL	12MONTHS		107	5.9	3.6		NORMAL
96	68/M	49	4.4	5.5		HYPOTHYROID	33MONTHS		39	4.1	13.6		HYPOTHYROID
97	52/M	96	4.9	4.1		NORMAL	8MONTHS		110	4.5	4.3		NORMAL
98	30/M	135	6.8	3.3		NORMAL	11MONTHS		130	6.5	4.2		NORMAL
99	42/F	95	4.9	2.7		NORMAL	12MONTHS		86	4.5	3.6		NORMAL
100	56/M	97	5.1	4.8		NORMAL	7MONTHS		107	4.9	5.1		NORMAL

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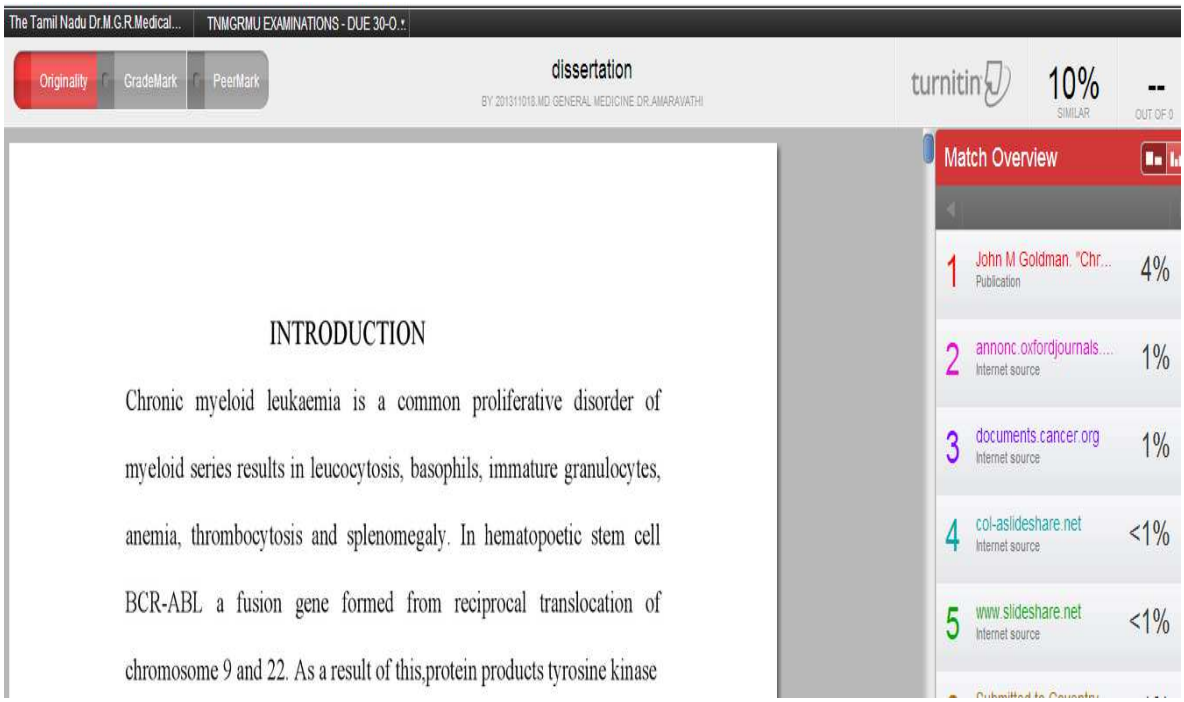
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INTRODUCTION
Chronic myeloid leukaemia is a common proliferative disorder of myeloid series results in leucocytosis, basophils, immature granulocytes, anemia, thrombocytosis and splenomegaly. In hematopoetic stem cell BCR-ABL a fusion gene formed from reciprocal translocation of chromosome 9 and 22. As a result of this,protein products tyrosine kinase
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