



Why Imatinib is by Far the Best Drug to Treat Chronic Myeloid Leukemia?

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Abstract

The objective of chronic myeloid leukemia treatment is to remove the platelets that contain the strange BCR-ABL gene that causes the high number of infected platelets. For the vast majority, it's unrealistic to dispose of every sick cell, yet treatment can accomplish a long haul remission of the disease. The meds utilized for patients with ceaseless (Chronic) stage interminable myelogenous leukemia (CML) go for postponing the onset of the quickened or blastic phase. This has generally incorporated a myelosuppressive operator to accomplish hematologic abatement, yet more compelling medications-progressively, interferon Alfa then and focused on treatment with tyrosine kinase inhibitors, for example, imatinib mesylate, have increased more noteworthy significance. Imatinib is a protein-tyrosine kinase inhibitor. It works by keeping the development of malignancy cells.

Keywords: *Chronic myeloid leukemia, Remission, Imatinib mesylate, Philadelphia chromosome, Translocation*

Introduction

Scientists are gaining awesome ground in seeing how changes in human DNA can make typical bone marrow cells form into leukemia cells. Finding out about changes in the qualities (locales of the DNA) required in CML is giving knowledge into why these cells become too rapidly, live too long, and don't grow into typical platelets. The blast of learning as of late is being utilized to create numerous new medications [1-3].

Chronic myeloid leukemia (CML), also known by the name Chronic myelogenous leukemia, is a sort of disease that begins in certain blood-forming cells of the bone marrow. In CML, a point mutation happens in an early (juvenile) variant of myeloid cells - the cells that make red blood cells, platelets, and most sorts of WBC (with the exception of lymphocytes) [4,5]. This change frames a strange quality called BCR-ABL, which transforms the phone into a CML cell. The leukemia cells develop and partition, developing in the bone marrow and overflowing into the blood. In time, the cells can likewise live in different parts of the body, including the spleen. CML is a genuinely slow developing leukemia; however it can likewise change into a quickly developing Acute Leukemia that is difficult to treat [6].

Normally, being listed as chronic shows that this sort of leukemia spreads and grow gradually. CML is not fatal if known earlier but it can be if not diagnosed early as this type of leukemia spreads slowly but can change to rapid growing leukemia, that can spread to anywhere in the body. Not like the three other type leukemia, CML has a huge distinction that separates it from the rest. It has been demonstrated that CML is somehow connected with a strange chromosome or chromosomal

abnormality named as Philadelphia chromosome (Ph chromosome) [7-10]. Chromosomes are thread like structures of DNA in cells that contain genetic information in the form of genes, which offer directions to the cells. The Ph chromosome is an irregularity that happens when a small bit of chromosome 22 cross over and connects to the end of chromosome 9, and small bit of chromosome 9 get attach to the end of chromosome 22 (called reciprocal translocation)during cell division. The breaks in both chromosomes cause the BCR and ABL qualities, which join to make the disease quality. The connection between the Ph chromosome and CML was found around 1960 [10-13].

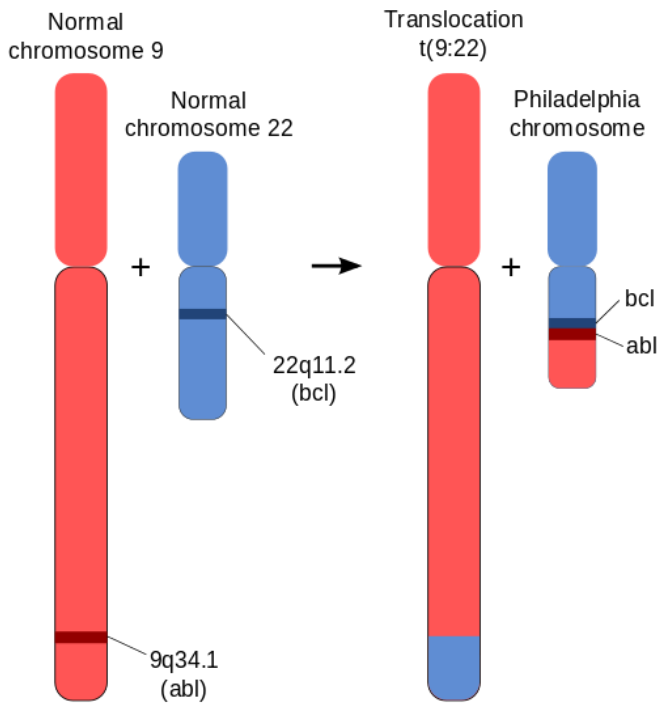


FIG. 1. Translocation of BCR-ABL gene in Chromosome 9 and Chromosome 22

Chemotherapy might be utilized, especially in planning for bone marrow or hematopoietic undeveloped cell transplantation. To control the fundamental hyper proliferation of the myeloid components, a myelosuppressive specialist is accustomed to cut down WBC numbers and, at times, hoisted platelet checks. Spleen size connects with WBC numbers, and it shrivels as WBC checks approach the reference range. Additionally, middle of the road and myeloblast cells vanishes from the course [14-17].

Tyrosine kinase inhibitors inspire solid hindrance of tyrosine kinase action of the BCR/ABL variation from the norm in all periods of CML [18].

Focused on medications

Focused on medications (Targeted Drugs) are intended to assault disease by concentrating on a particular part of malignancy cells that permits them to develop and increase. In interminable myelogenous leukemia, the objective of these medications is the protein created by the BCR-ABL quality-tyrosine kinase [19-22]. Focused on medications that piece the activity of tyrosine kinase includes:

- Imatinib (Gleevec)
- Dasatinib (Sprycel)
- Nilotinib (Tasigna)
- Bosutinib (Bosulif)
- Ponatinib (Iclusig)

Focused on medications is the underlying treatment for a great many people determined to have incessant myelogenous leukemia. On the off chance that the illness doesn't react or gets to be impervious to the initially focused on medication, specialists may consider other focused on medications, for example, omacetaxine (Synribo), or different medicines [23]. Symptoms of these focused on medications incorporate swelling or puffiness of the skin, queasiness, muscle spasms, rash, exhaustion, loose bowels, and skin rashes [24].

Specialists haven't decided a sheltered time when individuals with interminable myelogenous leukemia can quit taking focused on medications. Consequently, the vast majority keep on taking focused on medications notwithstanding when blood tests uncover an abatement of interminable myelogenous leukemia [25-30].

Blood Stem Cell transplant

A blood foundational microorganism transplant, additionally called a bone marrow transplant, offers the main chance for a complete cure for perpetual myelogenous leukemia. In any case, it's typically saved for individuals who haven't been aided by different medicines since blood undifferentiated organism transplants have dangers and convey a high rate of genuine entanglements [31,32].

Amid a blood undifferentiated organism transplant, high measurements of chemotherapy medications are utilized to murder the blood-framing cells in bone marrow. At that point blood undifferentiated cells from a contributor or own particular cells that were already gathered and put away are mixed into circulatory system. The new cells frame new, solid platelets to supplant the sick cells [30,33-35].

Chemotherapy

Chemotherapy medications are normally consolidated with different medicines for incessant myelogenous leukemia. Regularly, chemotherapy treatment for interminable myelogenous leukemia is given as a tablet orally. Symptoms of chemotherapy medications rely on upon what drugs are being taken [36,37].

Organic treatment

Organic treatments saddle the body's resistant framework to battle tumor. The natural medication interferon is a manufactured form of an insusceptible framework cell. Interferon may lessen the development of leukemia cells [38]. Interferon might be a choice if different medicines don't work or in the event that one can't take different medications, for example, amid pregnancy. Reactions of interferon incorporate weakness, fever, influenza like side effects and weight reduction [39,40].

Clinical trials

Clinical trials ponder the most recent treatment for ailments or better approaches for utilizing existing medicines. Enlisting in a clinical trial for interminable myelogenous leukemia may allow attempting the most recent treatment, yet it can't promise a

cure [41]. Consulting specialist about what clinical trials are accessible for this. Together examine the advantages and dangers of a clinical trial [42,43].

Imatinib Uses

Imatinib is also used for Treating other kind of leukemia, certain bone marrow disorders/diseases, skin malignancy, and certain intestinal tumors (e.g., GIST [gastrointestinal stromal tumors]). It might likewise be utilized to keep growth from developing in patients after surgical evacuation of GIST [44,45]. It is likewise used to treat mastocytosis (a development of a lot of pole cells in specific parts of the body) or hypereosinophilic disorder (a development of a lot of eosinophils in the body) [46-49].

Imatinib mesylate is known to be a protein-tyrosine kinase inhibitor that hinders the BCR-ABL tyrosine kinase, the constitutive irregular tyrosine kinase made by the Philadelphia chromosome variation from the norm in CML [50-55]. Imatinib restrains multiplication and incites apoptosis in BCR-ABL positive cell lines and additionally crisp leukemic cells from Philadelphia chromosome positive unending myeloid leukemia. Imatinib represses settlement arrangement in tests utilizing ex vivo fringe blood and bone marrow tests from CML patients [55-57].

In vivo, imatinib restrains tumor development of BCR-ABL transfected murine myeloid cells and also BCR-ABL positive leukemia lines got from CML patients in impact emergency [58].

Imatinib is likewise an inhibitor of the receptor tyrosine kinases for platelet-determined development component (PDGF) and undifferentiated organism variable (SCF), c-pack, and represses PDGF-and SCF-intervened cell occasions. In vitro, imatinib restrains expansion and actuates apoptosis in GIST cells, which express an enacting c-unit change [59-63].

Mechanism of Action

BCR/ABL is a perfect focus for atomic focused on treatment, as this fusion protein is available in the majority of the CML cells, is missing from nonmalignant cells, and is vital and adequate to incite leukemia. Imatinib mesylate-2-phenylaminopyrimidine tyrosine kinase inhibitor with particular action for ABL, platelet inferred development component receptor, c-pack, and Albeson-associated gene [64-69]. The pharmacological premise of this communication has been explained by crystallographic ponders. Imatinib mesylate attaches to the binding sites of amino acids of the BCR/ABL tyrosine kinase ATP and stabilizes the non-ATP-restricting type of BCR/ABL, preventing autophosphorylation of tyrosine and, thus, phosphorylation of its substrates is done. This procedure “switches off” the leukemogenesis that is done by shutting off downstream signaling pathways [70]. Preclinical in vitro and in vivo information demonstrated a noteworthy particular movement of imatinib mesylate on cells communicating BCR/ABL, and bolstered a fast move of this compound from the seat to the facility [71,72].

Imatinib mesylate has been assessed in a few Phase I and II clinical trials of patients with IFN- α -safe interminable, quickened, or BP CML (7, 8, 18, 19, 20). From the aggregate examination of these studies, imatinib mesylate appears to adequately initiate high CHR and cytogenetic reaction rates with generally few symptoms [73-75]. In patients with CP CML who have fizzled IFN- α , CHR was 95%, MCR 60%, and complete cytogenetic abatement 46%. Remarkably, in these patients accomplishment of MCR at the 3-month time point connected with enhanced movement free survival. In AP and in impact emergency, the CHRs were 34% and 8%, MCRs were 24% and 16%, and complete cytogenetic abatements were 17%, and 7%, individually. Ailment movement was 11% at year and a half for CP, 40% at 12 months for AP, and 80% at year and a half for BP. At long last, preparatory information from a break examination of a stage III investigation of untreated CML patients randomized between imatinib mesylate versus IFN- α and ARA-C show an altogether better CHR, complete

cytogenetic abatement, and movement free survival for the imatinib mesylate bunch after a middle follow-up of 14 months [76-78]. In any case, a more extended follow-up will be important to survey whether this compound can likewise effect on the regular history of the ailment and forestall or postpone change to impact emergency [79].

Side Effects of Imatinib

We have clarified the most widely recognized symptoms of imatinib. We have excluded those that are uncommon and unrealistic to influence an individual. Imatinib side effects are somehow moderate and very mild. They usually occur during the principal month of treatment and may improve after this. Specialist routinely checks whether the drug is working while patient is taking imatinib. Patient's consistent blood tests and weight will be checked [80-82].

Every individual's response to treatment is distinctive. A few people have not very many reactions, while others may encounter more. The symptoms portrayed here won't influence everybody having this treatment [83-85].

1. Nausea

This is normally mellow. Specialist can prescribe anti-emetic medications to counteract or decrease affliction and spewing. Intake of imatinib with meal can be helpful. If this not works Doctor give some other medication that suits patient some against ailment medications can bring about obstruction.

2. Diarrhoea

Imatinib can bring about loose bowels. This can ordinarily be controlled with medication. Specialist should be informed in the event that it's extreme or proceeds. It's imperative to drink a lot of liquids in the event that has looseness of the bowels.

3. Migraines

Imatinib can bring about migraines. In the event that patient has cerebral pains, Specialist or Doctor should be informed about this. They can prescribe a painkiller.

4. Leg aches/cramps

Doctors can prescribe medications to assuage any distress.

5. Build-up of fluid

This is genuinely normal. It's not hurtful, but rather can agitate. Many individuals put on weight or create swelling around the eyes and lower legs in view of liquid develop. Drugs that make one pass more pee (diuretics) can dispose of a portion of the liquid; however it regularly settles around itself. Let the doctor know if weight is increasing very quickly.

6. Effect on blood cells

Imatinib can lessen the quantity of platelets in the blood.

7. Risk of infection

If a patient has low WBC, he/she will probably get a contamination. Doctor or Specialist will encourage lessening danger of disease on the off chance that this happens. Specialist may request to quit taking tablets for a brief span, until white platelet numbers recuperate [86-89]. They may likewise request that take a lower measurement of imatinib.

Contact the Doctor straight away if:

- temperature goes more than 37.5°C (99.5° F) or more than 38°C (100.4° F)
- All of a sudden vibrate unwell, even with an ordinary temperature
- Indications of a disease- this can incorporate feeling temperamental, a sore throat, a hack, looseness of the bowels or expecting to pass pee a great deal [90].

8. Bruising and bleeding

Imatinib can diminish the quantity of platelets in the blood. Platelets are cells that help the blood to clot. Specialist should know the off chance that patient has any wounding or bleeding him/she can't clarify.

9. Anaemia

Imatinib can diminish the quantity of red platelets in the blood. On the off chance that the quantity of red platelets is low, patient might be drained and short of breath. Specialist or doctor should be informed.

10. Impacts on the eyes

Imatinib can bring about eye torment, dry or watery eyes or changes in vision.

11. Itchy rash

A few people build up a bothersome rash. It should be known by specialist in regarding whether this happens. They can recommend solution to offer assistance.

12. Loss of appetite

Patient may see changes in feeling of taste or lose Appetite while having imatinib. This can be mellow and may just last a couple days.

13. Difficulty sleeping

If it is hard to sleep let the Doctor know about this.

14. Tiredness (exhaustion)

Patient may feel more drained than expected during and after treatment. In the event that feel sluggish, don't drive or work hardware.

It's critical to tell the specialist straight away in the event that one feel unwell or have any extreme reactions, regardless of the possibility that they're not specified previously [91,92].

Why Only Imatinib

Management of treatment danger

We realize that both dasatinib and nilotinib require more watchful and general checking contrasted with IM. On development, CML patients on IM are generally observed with a solitary complete blood test; in any case, seeing the unfavorable occasion's list with nilotinib and dasatinib, it will be essential to screen the liver capacity tests, lipid profile, glucose levels, electrocardiogram, and mid-section X-beam, which adds to the expense [93,94].

Compliance issues

As in one study, harmfulness of dasatinib was more contrasted with IM, which prompted more medication intrusions and measurements changes. Likewise, nilotinib is required to be taken twice every day contrasted with once per day dosing for IM will require cautious thought of patient profile while choosing the treatment [95].

Cost-adequacy

Since bland IM is effortlessly accessible in India, and soon in different nations (as IM patent expiry will be in the year 2016) [93], the expense of dasatinib and nilotinib will be the principle obstacle for utilizing them as first-line treatment.

Lack of second decision after 2GTKI

If dasatinib and nilotinib is utilized as cutting edge, the primary alternative for second-line treatment will be undifferentiated organism transplantation as ponatinib has been pulled back from the business sectors because of extreme reactions. Thus, it will be imperative to have a decent key arrangement before choosing the treatment for a person [95].

Conclusion

Imatinib came as miraculous drug that can be called as life support to those who are in need. The trials looking at dasatinib and nilotinib are still in juvenile stages with no unmistakable advantage on survival, and all the more genuine reports are required to pick up certainty in regards to the treatment poisonous quality and clinical viability of these medications. Focused on treatment is the popular expression nowadays. 10 years back the development of tyrosine kinase inhibitor Imatinib not too far off, as the focused on treatment had caught the creative energy of everybody in the field of malignancy. It is urging to see a substantial number of patients getting alleviation from destructive CML malady and driving a decent personal satisfaction with the assistance of this medication. Be that as it may, sky is not the farthest point and now we have second and third era tyrosine kinase inhibitors.

REFERENCE

1. Liu J, Ryan D, Wei T, et al. Evaluation of vitamin D level and fatigue in acute leukemia patients undergoing chemotherapy. *J Leuk.* 2015;3:194.
2. Sharma RK, Puri V, Mutreja D, et al. Applicability of a single 5 color cytoplasmic markers tube as primary panel in routine immunophenotyping of acute leukemia. *J Blood Disord Transfus.* 2015;6:309.
3. Tanyildiz HG, Malbora B, Yesil S, et al. Vitamin b12 deficiency mimicking acute leukemia in a child. *J Clin Case Rep.* 2014;4:430.
4. Brahimi M, Saidi D, Touhami H, et al. The use of cd45/ ssc dot plots in the classification of acute leukemias. *J Hematol Thromb Dis.* 2014;2:e107.
5. Wong GC, Low JG, Chlebicka NL, et al. Invasive mould disease – predictive risk factors in acute leukemia patients receiving intensive chemotherapy and its impact on survival. *J Blood Disord Transfus.* 2013;4:156.
6. Dogan S, Kurtovic-Kozaric A, Hajrovic A, et al. Comparison of mll fusion genes expression among the cytogenetics abnormalities of acute myeloid leukemia and their clinical effects. *J Biom Biostat.* 2016;7:312.
7. Blanc K, Lefebvre A, Chapuis N, et al. Acute respiratory failure in a patient presenting t-cell prolymphocytic leukemia: specific leukemic lung involvement? *J Clin Respir Dis Care.* 2016;2:116.
8. Haggag R, Hussein O, El Moaty HA, et al. Study of plasma endostatin level in patients with acute myeloid leukemia. *Adv Oncol Res Treat.* 2016;1:107.
9. Zhu HH, Liu YR, Qin YZ, et al. CD34-Negative is Highly Associated with T (15;17). T(V; 11q23) and the NPM1-Mutation Subtypes in 343 Newly Diagnosed Patients with Acute Myeloid Leukemia. *Chemo Open Access.* 2016;5:200.

10. Elbedewy TA, Elashtokhy HE. The utility and applicability of chronic myeloid leukemia scoring systems for predicting the prognosis of egyptian patients on imatinib: Retrospective Study. *J Leuk.* 2016;4:210.
11. Tulara NK. Adult t cell leukemia/lymphoma in a 56 years old indian male with history of miliary koch's on anti-tubercular therapy. *Oncol Cancer Case Rep.* 2016;2:110.
12. Chang F, Shamsi TS, Waryah AM. Clinical and hematological profile of acute myeloid leukemia (aml) patients of sindh. *J Hematol Thrombo Dis.* 2016;4:239.
13. Barik S. Combination therapy for chronic lymphoid leukemia. *J Cancer Sci Ther.* 2016;8:078-079.
14. Cheng H, Huang CM, Qiu HY, et al. A new mutation identified in an imatinib and nilotinib resistant chronic myeloid leukemia patient. *Chemo Open Access.* 2016;5:193.
15. Kodidela S, Pradhan SC, Muthukumar J, et al. Genotype distribution of dihydrofolatereductase variants and their role in disease susceptibility to acute lymphoblastic leukemia in indian population: An Experimental and Computational Analysis. *J Leuk.* 2016;4:209.
16. Hummel HD, Topp MS, Chang ET, et al. Adverse events in adults with relapsed or refractory acute lymphoblastic leukemia (all): a literature review of recent clinical trials. *J Leuk.* 2016;4:208.
17. Frezzato F, Trimarco V, Visentin A, et al. Targeting bruton's tyrosine kinase in chronic lymphocytic leukemia at the crossroad between intrinsic and extrinsic pro-survival signals. *J Leuk.* 2016;4:207.
18. Olaya N, Corredor A, Gutierrez MF. Bovine leukemia: zoonosis associated with breast cancer in humans?. *J Med Surg Pathol.* 2016;1:110.
19. Xu M, Yang Y, Fu X, et al. Aggressive natural killer cell leukemia secondary to hodgkin lymphoma: a case report and review of the literature. *Chemo Open Access.* 2016;5:182.
20. Yi-Zhi J, Lai-Quan H, Gui-Ping S, et al. Life-threatening capillary leak syndrome in an adult with refractory acute myeloid leukemia during allogeneic transplantation: a case report and review of literature. *Transplant Rep .* 2015;1:101.
21. Essa N, El-Ashwah S, Denewer M, et al. autoimmune hemolytic anemia in a patient with acute myelomonocytic leukemia. *J Blood Disord Transfus.* 2016;7:336.
22. Babi MA, Jerdi SA, Gorman M. Bilateral borderzone infarcts in hypereosinophilic leukemia without proximal vessel stenosis. *J Neurol Neurophysiol.* 2016;7:349.
23. Dhar PK, Naskar TK, Majumder D. Analytical model for the assessment of efficiency of stem cell transplantation with suicidal gene construct for the treatment of leukemia. *Oncol Trans Res.* 2015;1:103.
24. Harif M. Hairy cell leukemia associated with a bone marrow tuberculosis. *J Cytol Histol.* 2016;7:382.
25. Ngaeje M, Chinenere F, Magessa A, et al. A case of a child with chronic myeloid leukemia presenting with vision and hearing loss. *J Blood Disord Transfus.* 2016;7:333.
26. Bhinder MTM, Halum AS, Muflih SM, et al. Pharmacogenetic testing for methotrexate treatment in leukemia patients. *J Biomol Res Ther.* 2016;4:134.
27. Agius LM. A dual origin for bcr-abl gene translocation/fusion as dynamics of synergism of the hematopoietic stem cell and hemangioblast in chronic myeloid leukemia. *J Leuk.* 2015;3:203.
28. Elbedewy TA, Elashtokhy HE. The Utility and Applicability of Chronic Myeloid Leukemia Scoring Systems for Predicting the Prognosis of Egyptian Patients on Imatinib: Retrospective Study. *J Leuk.* 2016;4:210.
29. Seddik Y, Brahmi SA, Afqir S. Interstitial Pneumonitis during Imatinib Therapy in a Patient with Gastrointestinal Stromal Tumor: A Case Report. *J Cancer Sci Ther.* 2015;7:269-271.

30. Azad NA, Baba SM, Shah ZA, et al. Phytohemagglutinin-Induced Peripheral Blood Cytogenetics: A Valid Means for Diagnosis and Imatinib Therapy Monitoring of Chronic Phase Chronic Myeloid Leukemia Patients. *J Cancer Sci Ther.* 2015;7:242-248.
31. Paolo CD, Minetti S, Mineni M, et al. Cutaneous Adverse Reactions to Imatinib: A Case Report of a Successful Slow Protocol for Induction of Drug Tolerance. *J Allergy Ther.* 2015;6:203.
32. Sampaio TS, Lima LM, da Silva Zardo R, et al. Synthesis. Antiproliferative and Anti-inflammatory Activities of Novel Simplified Imatinib Analogues. *Med chem.* 2014;4:756-762.
33. Shaikh MU, Moatter T, Syed NN, et al. Response to Imatinib Mesylate in Patients with Early Chronic Phase Chronic Myeloid Leukemia and Derivative Chromosome 9 Deletion or Clonal Evolution. *J Clin Exp Pathol.* 2014;4:166.
34. Skrivanova K, Bendova M, Dusek L, et al. The Effect of Imatinib Treatment Duration on the Quality of the Life of Patients with Chronic Myeloid Leukemia. *J Blood Disord Transfus.* 2013;4:167.
35. Achkar WAL, Moassass F, Ikhtiar A, et al. Cytogenetic Evolution in a Patient with Chronic developing a Secondary Acute Myelogenous Leukemia Subtype M5 Resistant to Imatinib Mesylate Therapy. *J Leuk (Los Angel).* 2013;1:118.
36. El Nagggar AA, Shama A, Zaki NE, et al. Bilateral Visual Loss in a Patient with Chronic Myelogenous Leukemia after Initiation of Imatinib Therapy. *J Leuk (Los Angel).* 2013;1:119.
37. Bay K, Bjerrum OW, Olsson-Strömberg U, et al. Reproductive Hormone Profiles during Imatinib Therapy in Men with Chronic Myeloid Leukemia. *Andrology.* 2013;2:105.
38. Gargantilla P, Arroyo N, Pintor E. Primary plasma cell leukemia presenting with chest pain. *J Hematol Thrombo Dis* 3:225.
39. Hassanein M Haggag R, El Shorbagy SM, et al. Prognostic value of hematogones in patients with acute myeloid leukemia in first complete remission. *J Blood Disord Transfus.* 2015;6:319.
40. Bahoush GR, Yazdi E, Ansari SH, et al. Identification of children with acute lymphoblastic leukemia at low risk for tumor lysis syndrome. *J Blood Disord Transfus.* 2016;6:318.
41. Kumar H, Raj U, Gupta S, et al. Systemic review on chronic myeloid leukemia: therapeutic targets. pathways and inhibitors. *J Nucl Med Radiat Ther.* 2015;6:257.
42. Elswawi R, Mohammed EAEM, Abogresha NM, et al. Using a simple. non-expensive in vitro model for studying chronic myeloid leukemia in research laboratories. *Clon Transgen.* 2016;4:145.
43. Zhang Q, Ding N, Xiong Q, et al. Regulatory roles of klf3 in hematopoiesis of k562 leukemia cells. *J Stem Cell Res Ther.* 2014;5:310.
44. Elhadary AMA, El-Aragi GM, Ahmed MM, et al. Assessment of cytogenetic instability and gene transcription of chronic myelogenous leukemia cells exposed to non-thermal plasma. *J Cytol Histol.* 2016;6:371.
45. Somasundaram V, Ahuja A, Manivannan P, et al. Unusual hairy projections in a case of t-acute lymphoblastic leukemia. a cause for diagnostic dilemma: a case report. *J Hematol Thrombo Dis.* 2015;3:223.
46. Gargantilla P, Arroyo N, Pintor E. leukemia and origami crane. *J Hematol Thrombo Dis.* 2015;3:217.
47. Elbossaty WE, Malak C, Elghanam DM. Prognostic relevance of ww-oxidoreductase gene expression in patients with acute lymphoblastic leukemia. *J Cancer Sci Ther.* 2015;7:302-307.
48. Gadhia P. Three way philadelphia variant in chronic myeloid leukemia. *J Leuk.* 2015;3:191.
49. Atfy M. CD200 Suppresses the natural killer cells and decreased its activity in acute myeloid leukemia patients. *J Leuk.* 2015;3:190.
50. Reure J, Peyrade F, Lebrun-Frenay C, et al. Posterior reversible encephalopathy syndrome during induction treatment of philadelphia positive acute lymphoblastic leukemia in an adult patient: first case report and literature review. *J Blood Lymph.* 2015;5:141.

51. Neanaa H, Hamed NA, Raafat A, et al. Comparative study between valproic acid combined with conventional chemotherapy versus conventional chemotherapy alone in egyptian acute myeloid leukemia patients. *J Blood Lymph.* 2015;5:140.
52. Ribers JM. Blinatumomab: a promising new drug in the therapeutic armamentarium for acute lymphoblastic leukemia. *Chemo Open Access.* 2014;4:164.
53. Leite LAC, Magalhães AG, Silva JF, et al. Acute abdominal pain revealing a primary plasma cell leukemia: a rare and aggressive case of plasma cell dyscrasia. *J Cytol Histol.* 2016;6:364.
54. Bülbül, Dursun M, Yildirmak Y, et al. Spontaneous remission in congenital leukemia aml-m1 with pericardial effusion. *J Neonatal Biol.* 2014;4:196.
55. Hela BJ, Sayda M, Nesrine G, et al. Recurrent ischemic cerebrovascular accidents with recurrent acute ischemia of the left upper limb revealing acute myeloid leukemia . *J Vasc Med Surg.* 2015;3:209.
56. Mansour SA. E-cadherin immunohistochemistry stain and acute erythroid leukemia. the emerging story. *J Cytol Histol.* 2015;6:352.
57. Pennisi A, Jewell S, Gralewski J, et al. Acute lymphoblastic leukemia evolving from atypical chronic myelogenous leukemia: case report and review of the literature. *J Leuk S.* 2016;1:007.
58. Chi J, Costeas P. The evolution of genetics techniques for leukemia diagnosis. *Adv Tech Biol Med.* 2016; 3:e111.
59. Hamid GA. Treatment development of chronic myeloid leukemia. *J Develop Drugs.* 2015;4:e144.
60. Robak T. Bcl-2 inhibitors for chronic lymphocytic leukemia. *J Leuk.* 2016;3:e114.
61. Yokus, Gedik H. Severe neurological signs due to hyponatremia in patient with acute myeloid leukemia; ethiological factors and therapeutic approach. *J Blood Disord Transfus.* 2015;5:001.
62. Okuno N, Terahata S, Sugiguchi S, et al. A case of t-cell prolymphocytic leukemia/lymphoma suggested thyroid origin. *thyroid disorders ther .* 2016;4:190
63. Pathak P. The changing therapeutic landscape of chronic lymphocytic leukemia. *J Blood Lymph.* 2015 5:e120.
64. Yahia S, El-Hadidy MA, El-Gilany AH, et al. Cognitive function and quality of life in egyptian children with acute lymphoblastic leukemia. *J Blood Disord Transfus.* 2015;6:291.
65. Balci Y, Polat A, Sarbay H, et al. Mature b cell acute lymphoblastic leukemia presenting with hypercalcemia. *J Leuk.* 2015;S1:002.
66. Kaleem B. Plasma cell leukemia-behind a disguise. *J Clin Case Rep.* 2015;5:533.
67. Takemoto S, Pornkuna R, Nishioka C. Serum Soluble CD30 Levels to Detect Activation and Aggression Status of Adult T-Cell Leukemia/Lymphoma Cells. *J Hematol Thrombo Dis.* 2015;3:205.
68. Kallus SJ, George NB. A Case of Hypergranular Acute Promyelocytic Leukemia (French-American-British Classification M3) Neil Batta. MS3. *J Clin Case Rep.* 2015;5:i105.
69. Reksodiputro AH, Tadjoeidin H, Supandiman I, et al. Epidemiology Study and Mutation Profile of Patients with Chronic Myeloid Leukemia (CML) in Indonesia. *J Blood Disord Transfus* 2015;6:271.
70. Druhan L, Fasan O, Copelan OR. Acute Heart Failure in a Patient with Acute Myeloid Leukemia following Daunorubicin Treatment: a Case Report. *J Leuk.* 2015;3:185.
71. Knauf W. Chronic Lymphocytic Leukemia: Raising Expectations in the Treatment of Elderly Patients. *J Leuk.* 2015;3:181.
72. Breccia Massimo, Molica M, Colafigli G, et al. Early molecular response in chronic myeloid leukemia and halving time: Latest evidences. *Leuk Res.* 2015;48:20-25.
73. Alves APNR, Machado-Neto AG, Scheucher PS, et al. Reversine triggers mitotic catastrophe and apoptosis in K562 cells. *Leuk Res.* 2015;48:26-31

74. Beatriz B, Alvarez-Larrán A, Bellosillo B, et al. Characterization of CD34+ hematopoietic progenitor cells in JAK2V617F and CALR-mutated myeloproliferative neoplasms. *Leuk Res* 2015;48:11-15.
75. Salma Al Dallal, Wolton K, Hentges KE. Zfp521 promotes B-cell viability and cyclin D1 gene expression in a B cell culture system. *Leuk Res*. 2016;46:10-17
76. Wang Q, Li Y, Cheng J, et al. Sam68 affects cell proliferation and apoptosis of human adult T-acute lymphoblastic leukemia cells via AKT/mTOR signal pathway. *Leuk Res*. 2015;46:1-19.
77. Hernández-Sánchez M, Ana E. Rodríguez-Vicente. MiRNA expression profile of chronic lymphocytic leukemia patients with 13q deletion. *Leuk Res*. 2015;46:30-36
78. Zhang H, Chen L, Cai SH, et al. Identification of *tbk1* and *ikke*. the non-canonical *ikb* kinases. as crucial pro-survival factors in *htlv-1*-transformed t lymphocytes. *Leuk Res*. 2015;46:37- 44.
79. Mian Y, Zeleznik-Le N. The miR-17~92 cluster contributes to MLL leukemia through the repression of MEIS1 competitor PKNOX. *Leuk Res*. 2015;146:51-60.
80. Cao XX, Meng Q, Mao YY, et al. The clinical spectrum of IgM monoclonal gammopathy: A single center retrospective study of 377 patients. *Leuk Res*. 2015;46: 85 -88.
81. Manzoni D, Catallo R2, Chebel A, et al. The ibrutinib B-cell proliferation inhibition is potentiated in vitro by dexamethasone: Application to chronic lymphocytic leukemia research. *Leuk Res*. 2015;47:1-7.
82. Yamaguchi T, Ishiyama K, Eto T, et al. Acute megakaryoblastic leukemia. unlike acute erythroid leukemia. predicts an unfavorable outcome after allogeneic HSCT. *Leuk Res*. 2015;47:47-53.
83. Jing XM, Zhang ZH, Wu P, et al. oxaliplatin with sandwiched radiotherapy in the treatment of newly-diagnosed extranodal nature killer (NK)/T cell lymphoma. *Leuk Res*. 2015;47:26-31.
84. Niemöller C, Renz N, Bleul S, et al. Single cell genotyping of exome sequencing-identified mutations to characterize the clonal composition and evolution of *inv(16)* aml in a *cbl* mutated clonal hematopoiesis leukemia research. *Leuk Res*. 2015; 47:41-46.
85. Tang FF, Huang XJ, Zhang XH, et al. Allogeneic hematopoietic cell transplantation for adult patients with treatment-related acute myeloid leukemia during first remission: Comparable to de novo acute myeloid leukemia. *Leuk Res*. 2015;47:8-15.
86. XU X, He Y, Miao X, et al. Cell adhesion induces overexpression of chromodomain helicase/ATPase DNA binding protein 1-like gene (CHD1L) and contributes to cell adhesion-mediated drug resistance (CAM-DR) in multiple myeloma cells. *Leuk Res*. 2015;47:54-62.
87. Heinz T, Bennett JM, Aul C, et al. Dysplastic erythroid precursors in the myelodysplastic syndromes and the acute myeloid leukemias: Is there biologic significance? (How should blasts be counted?). *Leuk Res*. 2015;47:63-69.
88. Heim D, Medinger M, Gerull S, et al. Increase of endothelial progenitor cells in acute graft-versus-host disease after allogeneic haematopoietic stem cell transplantation for acute myeloid leukemia . *Leuk Res*. 2015;47:22-25.
89. Wang J, Hu J, Jin Z, et al. The sensitivity of chronic myeloid leukemia CD34 cells to Bcr-Abl tyrosine kinase inhibitors is modulated by ceramide levels. *Leuk Res*. 2015;47:32-40.
90. Eidukaite A, Stoskus M, Griskevicius L. Laimonas Griskevicius. Defining the significance of IGF2BP1 overexpression in t (12;21)(p13;q22)-positive leukemia REH cells. *Leuk Res*. 2016;47: 16-21.
91. Shirai Y, Miyashita M, Kawa M, et al. Evaluation of care for leukemia and lymphoma patients during their last hospitalization from the perspective of the bereaved family. *Leuk Res*. 2015;47:93-99.
92. Aqil B, Punia JN, Curry V, et al. Are micromegakaryocytes specific for refractory cytopenia of childhood (RCC)? A study of 38 pediatric patients with thrombocytopenia unrelated to RCC. *Leuk Res*. 2015; 47: 84–87.
93. Bansal S. Is imatinib still the best choice as first-line oral TKI. *South Asian J Cancer*. 2014;3:83-86.

94. Chatterjee R, Chattopadhyay S, Law S. Alteration of classical and hematopoiesis specific p53 pathway in the bone marrow hematopoietic stem/progenitor compartment facilitates leukemia progression in experimental mice. *Leuk Res.* 2015;47:70-77.
95. Tang Z, Li Y, Wang SA, et al. Clinical significance of acquired loss of the X chromosome in bone marrow. *Leuk Res.* 2015;47:109.