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The Philadelphia Chromosome Detection in Chronic Myeloid Leukemia in Karbala City

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Abstract:

Background: The mutual transposition t (9;22) (q34; q11) results in the Philadelphia chromosome (Ph), which is an ideal marker of chronic myeloid leukemia (CML). The proto-oncogene tyrosine-protein kinase (BCR-ABL1) oncogenic breakpoint cluster region-protein with enhanced tyrosine kinase action is encoded by this fusion gene. The kinase movement is measurable for cell proliferation, diversity inhibition, and cell death confrontation. Styles of representation in isolate BCR-ABL1 transcripts change when CML progresses transitioning from a chronic to an expedited phase and ultimately to the blast phase. Every BCR-ABL1 transcription is concomittant with a specific leukemia phenotype that expects treatment clinical outcome and reaction prognosis. The Ph is seen in acute lymphoblastic leukemia, acute myeloid leukemia, and motley-type acute leukemia, in addition to CML.

Aim of the study: to give a view of the clinical diagnostic importance of Philadelphia chromosome CML and role of Philadelphia in comparison to morphology.

Methods: A total of 180 patients had developed leukocytosis with severe Lf-shift by blood film. Data for patients, as age and sex, were collected. Blood samples, including CBC with total WBC, and differential counts, were performed using 5-parts differential URIT autoanalyzer hematology.

Results: A total of 180 patients with leukocytosis, 150 of them had Philadelphia chromosome-positive with a mean age of 52.86 ± 13.9 (range: 29-80) years were collected. Sixty (50%) cases were male and sixty % were female and 30 cases of them were Philadelphia negative with a mean age of 56.1 ± 14.8 years, 17 cases were male and 13 cases were female. There was an important difference between the two groups. In this study, the mean ±SD for Philadelphia positive patients was found to be a very highly significant difference when compared with Philadelphia negative group, at the level of significance (<0.001) by student T-Test.

Conclusion: The research of myeloproliferative disorders has many goals: diagnostic, therapeutic, predictive and follow-up, all of which contribute to better outpatient therapy.

Keywords: Chronic myeloid leukemia, BCR-ABL, Philadelphia chromosome.

INTRODUCTION

Chronic myeloid leukemia (CML) is the one of adult hematological cancer which is the most common kind that has the greatest mortality rate [1, 2]. Chronic myeloid leukemia (CML) is a

neoplastic granulocytic enhanced production described by monoclonal proliferation of the pluripotent stem cell. This myeloproliferative condition has two distinct characteristics: A chronic phase precedes an acceleration phase, which is followed by an acute (or explosion) alteration [3, 4].

The Philadelphia chromosome (Ph) is the translocation t(9;22)(q34;q11) reciprocally that was initially diagnosed in a CML patient in 1960 [5]. When the proto-oncogene tyrosine-protein kinase (ABL1) gene on chromosome 9 is moved to the cluster region (BCR) gene on chromosome 22, a BCR-ABL1 fusion gene is synthesized on the Ph. [6, 7]. TKIs that target the BCR-ABL1 protein are the most specific targeting treatment for Ph-positive leukemia [8, 9]. To help patients with Ph-positive leukemia have a better prognosis, treatment resistance and disease progression are the goals [10-12]. Ph is not only found in CML; it can also be found with acute myeloid leukemia (AML) [13-15], ALL [16], mixed-phenotype acute leukemia (MPAL), and acute lymphoblastic leukemia (ALL; all B-cell ALL, rare T-cell ALL). Patients with unique leukemia characteristics have varying prognoses as a result of Ph mutations [17–19].

Small chromosomal defects can be detected using molecular cytogenetics (semi-cryptic) that are not evident on metaphase chromosomes. The examination of differences that have developed is very important, and it is used to screen an aberrant clone's persistence for potential recurrent translocations. It may also be used to describe genes in the present carcinogenesis process [20].

Prognostic importance of Philadelphia chromosome in CML

It is possible to establish the likely time conversion of an explosion initiation when assessing the prediction of CML, which is similar to defining the likely period of the prolonged stage [21].

Enduring disease

The amount of cancerous cells present following cytotoxic therapy, whose eradicative activity is meant to be as comprehensive as feasible, is referred to as residual disease: Chemotherapy, ionizing radiation, and bone attaching are some of the treatments available. The remaining malignant cells that escape treatment can induce a relapse, thus it's critical to measure them as precisely as possible [22-25]. Hematologists had a variety of approaches to characterize the biotic recovery of homeopathy before the emergence of molecular biology: cytology, genetic analysis, and immunology. In the ideal circumstance, because their awareness approaches did not allow for the detection of extremely low sensibility criterion is less than one remnant cell in 100 for assisting clinicians in determining appropriate treatment and evaluating graft quality control [24, 31]. For example, in chronic myeloid leukemia, the therapies to be completed in instruction to achieve hematological reduction and, if feasible, total Ph1 (+) cells must be eradicated (cytogenetic remission) [32]. The progression occurred in two stages: A chronic phase that is well controlled by standard therapies is followed by a second transition phase known as resistance to traditional treatment has accelerates the process, after which undergoes an acute change, usually of the kind final severe myelogenous leukemia, which is always lethal and occurs 3 to 4 years following diagnosis is the norm [26, 27, 33].

MATERIAL AND METHODS

This study was retrospective, conducted on patients at Al-Aula private laboratory in Karbala city/Iraq, from 11/2021 to 3/2022, 180 patients developed leukocytosis with severe Lf-shift. Data for patients as age and sex, were collected from medical records. Blood samples were collected from all patients, including CBC with total WBC, Hb-level, and platelet counts were performed using 5-parts differential URIT autoanalyzer hematology. Blood film and BMA (bone marrow aspirate) were examined by light microscope after staining by Leishman stain & Philadelphia chromosome by (RT-PCR) tests were done. Results including WBC, Hb-level, platelets count & Philadelphia chromosome results were compared on graphs.

Statistical analysis

Statistical analysis was performed using excel. The mean standard deviation (mean SD) is used to represent measurement data having a normal distribution. For continuous variables that were normally distributed, differences between the two groups were compared using the t-tests.

Criteria of selection:

1. Patients have leukocytosis.
2. Patients suspected to have chronic myeloid leukemia on blood film & bone marrow study (aspirate & biopsy) (where they admitted to oncology unit).
3. Patients have leukemia symptoms (fever, splenomegaly, hepatomegaly, lymphadenopathy & other leukemia symptoms).
4. Age (12-90) years old (adults).

RESULTS

The total patients were 180 with leukocytosis and Lf-shift, 150 of them had Philadelphia chromosome-positive with a mean age of 52.86 ± 13.9 (range: 29-80) years were collected. Eighty (50%) cases were male and eighty % were female and 30 cases of them were Philadelphia negative with a mean age of 56.1 ± 14.8 years, 17 cases were male and 13 cases were female. There was a significant difference between the two groups (Table 1).

Table 1: Patients' variables mean in Philadelphia chromosome-positive and negative

Variables	Phil. +ve (n=150) (M ± SD)	Phil. -ve (n=30) (M ± SD)	*P*
Age	52.86 ± 13.9	56.1 ± 14.8	0.362
Total WBC (cells/mm^3)	104.3 ± 13.4	30.4 ± 0.5	<0.001
Hb (gram/dl)	9.3 ± 0.4	10.8 ± 0.1	<0.001
Platelets count (X109/L)	119.2 ± 1.4	145.9 ± 2.5	<0.001
Phil I.S.%	17.4 ± 2.4	5.8E-05±1.68 E-05	<0.001

In this study, the mean ±SD for Philadelphia chromosome I.S.% positive patients (17.4 ± 2.4) was found to be a very highly significant difference when compared with Philadelphia chromosome-negative patients (5.8E-05±1.68E-05), at the level of significance (<0.001) by student T-Test as shown in the figure (1).

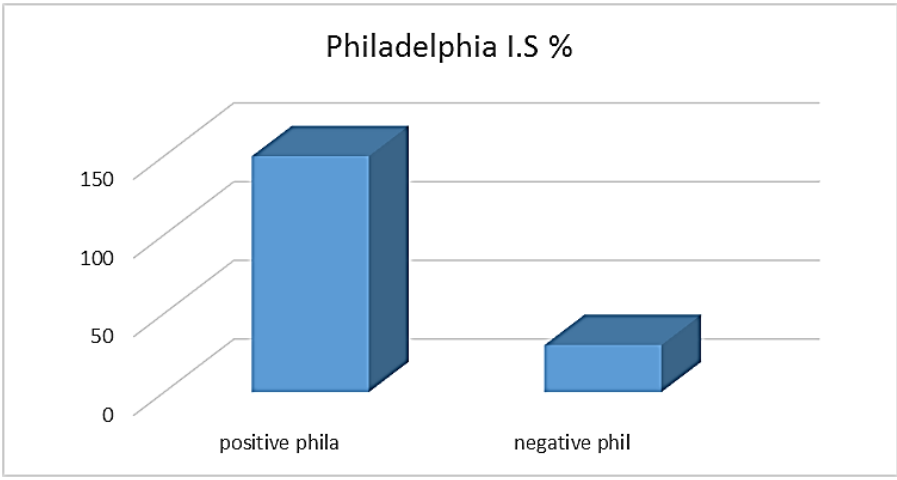

Figure 1: The mean I.S % Philadelphia chromosome-positive & negative patients.

WBC levels were higher in positive Philadelphia cases than in the negative Philadelphia group, and this difference was very high and significant. The mean ± SD for WBC of the patients (104.3 ± 13.4) was found to be when compared with the negative group (30.4 ± 0.5), at the level of significance (<0.001) by student T-Test as shown in figure (2).

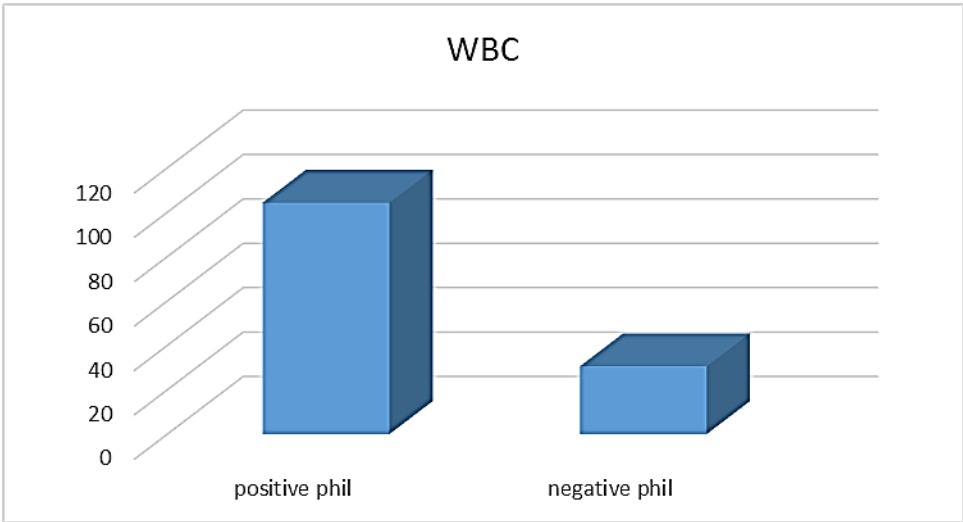

Figure 2: The mean WBC in positive & negative patients.

In this study, the mean ±SD for a Hemoglobin level of the positive Philadelphia cases (9.3 ± 0.4) was found to be significantly different when compared with the negative Philadelphia group (10.8 ± 0.1), at the level of significance (P=0.001) by student T-Test as shown in the figure (3).

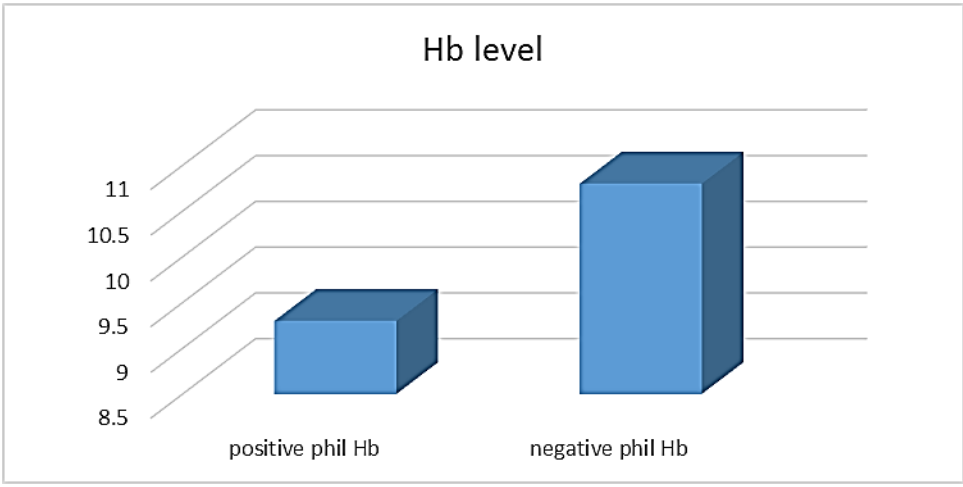

Figure 3: The mean Hb in positive & negative patients

In this study, the mean ±SD for platelets count of the positive Philadelphia cases (119.2 ± 1.4) was found to be significantly different when compared with the negative Philadelphia group (145.9 ± 2.5), at the level of significance (P=0.001) by student T-Test as shown in the figure (4).

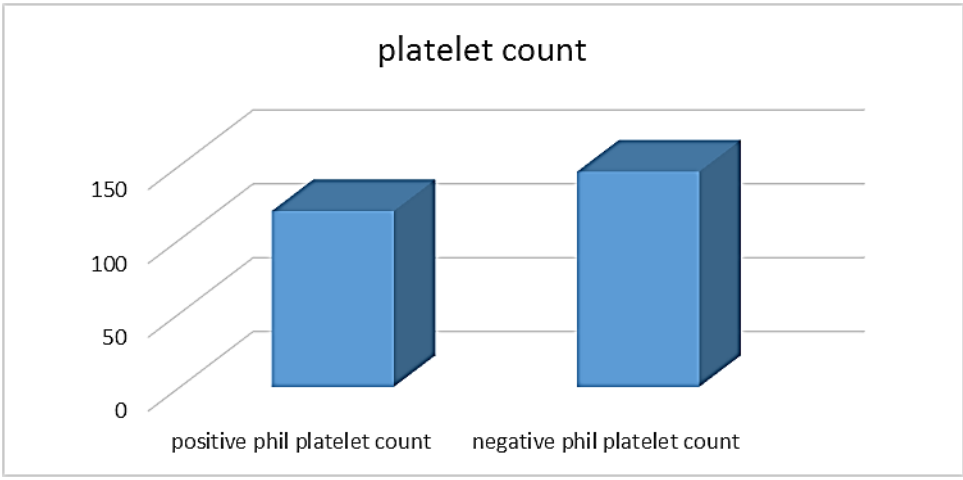

Figure 4: The mean platelet count in positive & negative patients

In this study, the mean ±SD for the age of the positive Philadelphia cases (52.86 ± 13.9) was found to be non-significantly different when compared with the negative Philadelphia group (56.1 ± 14.8), at the level of significance (P=0.001) by student T-Test as shown in the figure (5).

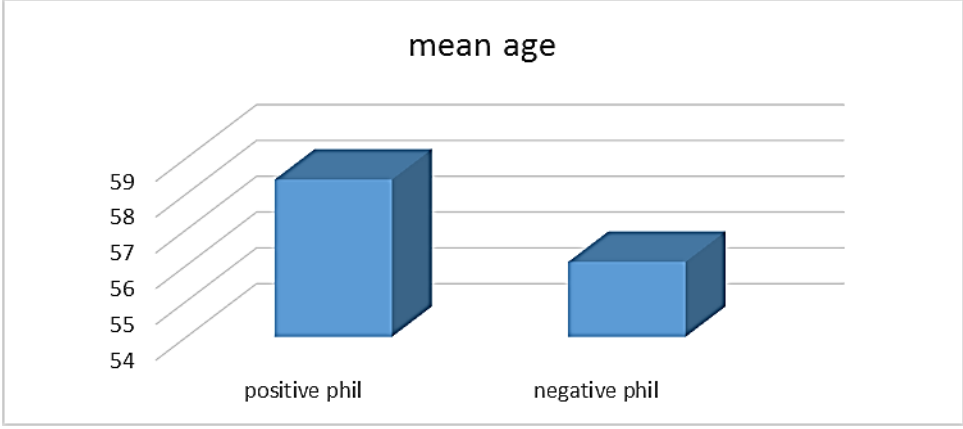

Figure 5: The mean age of the positive and negative Philadelphia groups.

In this study the distribution of the positive Philadelphia patient's sex is equal, 75 patients are male and 75 patients are female as shown in figure (6), while the distribution of the negative Philadelphia chromosome sex is unequal, 17 patients were male and 13 patients were female as shown in the figure (7).

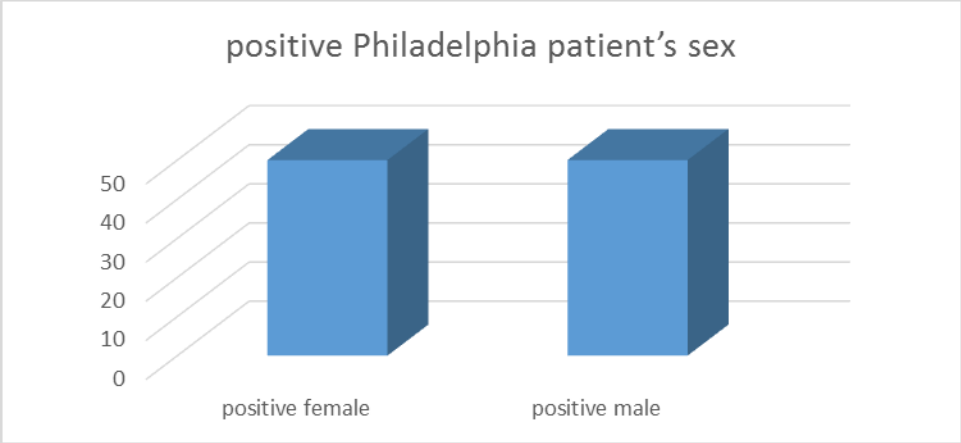

Figure 6: positive Philadelphia patients' sex

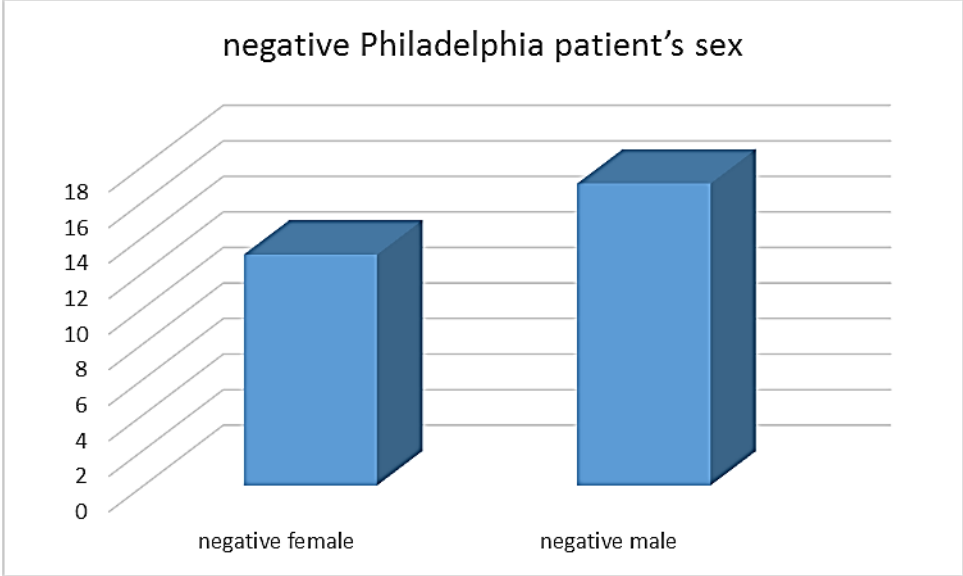

Figure 7: negative Philadelphia patient's sex

DISCUSSION

Philadelphia chromosome is a marker that is highly useful for diagnosis, prognosis, and follow-up in patients with chronic myeloid leukemia [3]. The findings have proven the hypothesis of the present study and suggest that the positive Philadelphia chromosome has a diagnostic importance marker that is complementary to morphological examination. Previous studies supported these findings [18, 19]. The chromosomal Ph is a characteristic of CML, and its detection is critical for the disease's identification. The Ph chromosome is else used by way of a marker for assessing interferon treatment or BMT reaction to therapy. Interferon therapy frequently results in a full cytogenetic response in patients [21].

CML patients do not have any symptoms when they are first diagnosed. An abnormal white blood cell count is the most prevalent symptom of CML, which is often discovered during blood tests [22].

Differential CBC (Complete Blood Count)

The test determines the number of erythrocytes, leukocytes, and thrombocytes in a blood test. So it calculates the quantity of hemoglobin in red blood cells and the ratio of red blood cells in the sample. In the CBC, a variance should be mentioned. The different counts of all of the distinct kinds of white blood cells in the sample.

Almost CML patients suffer from:

- ✓ An elevated white blood cell count, which can be fatal.
- ✓ According to the severity of the CML, the number of platelets may raise or reduce.

The study findings indicate that the complentation of Philadelphia chromosome detection and morphological examination of blood film & Bone marrow examination may lead to prediction improvement and is thus recommended as a important diagnostic marker & to predict prognosis.

BCR-ABL is a gene aberrantly produced by Ph+ CML. Tyrosine kinase is an aberrant protein produced by this gene in the bone marrow. This protein can activate the bone marrow, enabling it to produce an excessive number of immature white blood cells. Similar results were found by [23, 29, 30,].

The body normally produces and utilizes immature white blood cells in a controlled manner. Ph+ CML, on the other hand, causes these immature white blood cells to proliferate out of control. The Philadelphia chromosome can be found in these cells, which suggests that the copies of these cells will also have it [30].

A chromosome 9 fragment containing the oncogene ABL gets moved to chromosome 22 and joined to the BCR gene during this translocation. Oncoprotein bcr-abl tyrosine kinase is synthesized by the chimeric fusion gene BCR-ABL. The oncoprotein bcr-abl has unregulated tyrosine kinase activity, which lead to cellular growth inhibitions, reduces leukemia cell adhesion to the stroma, and shields malignant cells from normally scheduled cell death (apoptosis) [28, 30].

CONCLUSION

The research on myeloproliferative disorders has many goals: diagnostic, predictive, and therapeutic follow-up, all of which contribute to better outpatient therapy.

REFERENCES

1. Apperley JF. Chronic myeloid leukaemia. Lancet. 2015;385:1447–1459.
2. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin. 2015;65(1):5–29.
3. Höglund M, Sandin F, Simonsson B. Epidemiology of chronic myeloid leukaemia: an update. Ann Hematol. 2015; 94 Suppl 2:S241–S247.
4. Nikhitha P.M, Sunil. M, Deepu. Prasad. A Study to Assess the Knowledge and Illness Perception of Parents of Children with Leukemia, Attending Oncology units, at AIMS, Kochi. Int. J. Nur. Edu. and Research 3(4): Oct.-Dec., 2015; Page 344-350.

5. Chen W, Zheng R, Zeng H, Zhang S. The updated incidences and mortalities of major cancers in China, 2011. *Chin J Cancer*. 2015; 34(3):53.
6. Protein tyrosine kinase Abl promotes hepatitis C virus particle assembly via interaction with viral substrate activator NS5A.Miyamoto D, et al. J Biol Chem, 2022 Apr. PMID 35257746, Free PMC Article
7. ABL allosteric inhibitors synergize with statins to enhance apoptosis of metastatic lung cancer cells. Luttman JH, *et al*. Cell Rep, 2021 Oct 26. PMID 34706244, Free PMC Article.
8. Fielding AK, Rowe JM, Richards SM, et al. Prospective outcome data on 267 unselected adult patients with Philadelphia chromosome-positive acute lymphoblastic leukemia confirms superiority of allogeneic transplantation over chemotherapy in the pre-imatinib era: results from the International ALL Trial MRC UKALLXII/ECOG2993. *Blood.* 2009; 113:4489–4496.
9. Sangeeta Mahaur, Sukirti Upadhyay, Ravi Raj Pal. Indolizine: In-Silico Identification of Inhibitors against Mutated BCR-ABL Protein of Chronic Myeloid Leukemia. Res. J. Pharmacology and Pharmacodynamics.2020; 12(4):151-158.
10. Ottmann OG, Druker BJ, Sawyers CL, Goldman JM, Reiffers J, Silver RT, et al. A phase 2 study of imatinib in patients with relapsed or refractory Philadelphia chromosome-positive acute lymphoid leukemias. Blood. 2002; 100(6): 1965–1971.
11. Sawyers CL, Hochhaus A, Feldman E, Goldman JM, Miller CB, Ottmann OG, et al. Imatinib induces hematologic and cytogenetic responses in patients with chronic myelogenous leukemia in myeloid blast crisis: results of a phase II study. Blood. 2002; 99(10): 3530–3539.
12. Tojo A, Usuki K, Urabe A, Maeda Y, Kobayashi Y, Jinnai I, et al. A Phase I/II study of nilotinib in Japanese patients with imatinib-resistant or -intolerant Ph + CML or relapsed/refractory Ph + ALL. Int J Hematol. 2009; 89(5): 679–688.
13. Corbin AS, Agarwal A, Loriaux M, Cortes J, Deininger MW, Druker BJ. Human chronic myeloid leukemia stem cells are insensitive to imatinib despite inhibition of BCR-ABL activity. J Clin Invest. 2011; 121(1): 396–409.
14. Rafiei A, Mian AA, Doring C, Metodieva A, Oancea C, Thalheimer FB, et al. The functional interplay between the t(9;22)-associated fusion proteins BCR/ABL and ABL/BCR in Philadelphia chromosome-positive acute lymphatic leukemia. PLoS Genet. 2015; 11(4): e1005144.
15. Zhang LJ, Gan YM, Yu L. Occurrence of BCR/ABL fusion gene in a patient with acute promyelocytic leukemia. Med Oncol. 2015; 32(1): 382.
16. Verrma SP, Dutta TK, Vinod KV, Dubashi B, Ariga KK. Philadelphia chromosome positive pre-T cell acute lymphoblastic leukemia: a rare case report and short review. Indian J Hematol Blood Transfus. 2014; 30(Suppl 1): 177–179.
17. Choi W, Kim M, Lim J, Han K, Lee S, Lee JW, et al. Four cases of chronic myelogenous leukemia in mixed phenotype blast phase at initial presentation mimicking mixed phenotype acute leukemia with t(9;22) Ann Lab Med. 2014; 34(1): 60–63.
18. Matutes E, Pickl WF, Van't Veer M, Morilla R, Swansbury J, Strobl H, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Blood. 2011; 117(11): 3163–3171.
19. Sabattini E, Bacci F, Sagramoso C, Pileri SA. WHO classification of tumours of haematopoietic and lymphoid tissues in 2008: an overview. Pathologica. 2010; 102(3): 83–87.
20. Matutes E, Pickl WF, Van't Veer M, et al. Mixed-phenotype acute leukemia: clinical and laboratory features and outcome in 100 patients defined according to the WHO 2008 classification. Blood 2011; 117:3163.

21. Reikvam H, Hatfield KJ, Kittang AO, Hovland R, Bruserud Ø. Acute myeloid leukemia with the t (8;21) translocation: Clinical consequences and biological implications. J Biomed Biotechnol 2011;2011:104631

22. M. Sravani, N. Duganath, Deepak Reddy Gade, Sandeep Reddy C.H.. Insilico Analysis and Docking of Imatinib Derivatives Targeting BCR-ABL Oncoprotein for Chronic Myeloid Leukemia. Asian J. Research Chem. 5(1): January 2012; Page 153-158.

23. Mohamed Zerein Fathima, T.S. Shanmugarajan, S. Satheesh Kumar, B.V.Venkata Nagarjuna Yadav. Comparative in Silico Docking Studies of Hinokitiol with Sorafenib and Nilotinib against Proto-Oncogene Tyrosine-Protein Kinase(ABL1) and Mitogen-activated Protein Kinase (MAPK) to Target Hepatocellular Carcinoma. Research J. Pharm. and Tech. 2017; 10(1): 257-262.

24. Balakrishnan Purushothaman, Nagarasan Suganthi , Arunachalam Jothi, Kumaran Shanmugam. Molecular Docking Studies of potential anticancer agents from Ocimum basilicum L. against human colorectal cancer regulating genes: An insilico approach. Research J. Pharm. and Tech. 2019; 12(7): 3423-3427.

25. Jean-Claude Chomel and Ali G., Turhan Chronic myeloid leukemia stem cells in the era of targeted therapies: resistance, persistence and long-term dormancy , Oncotarget. 2011 Sep; 2(9): 713–727

26. Kiranmai Gudimetla, Orsu Prabhakar, Abhisek Pal. Review on Pathophysiological and Pharmacotherapeutic approach on Chronic Myeloid Leukemia. Research J. Pharm. and Tech 2020; 13(6): 2971-2976.

27. Ankit Darji, Praful Bharadia. Studies on the Quantification of Mutation Resistance to Specific Drug Therapy in Chronic Myeloid Leukemia patients. Research Journal of Pharmacy and Technology. 2021; 14(8):4092-0.

28. Sandip S. Kshirsager, Dr. Siraj N. Shaikh, Narendra B. Patil, Ketan B. Patil. Novel Molecule of Protein Tyrosine Kinase Enzyme Inhibitor in Treatment of Breast Cancer: Neratinib Maleate. Asian J. Res. Pharm. Sci. 2020; 10(2):100-102.

29. P. Ravi Sankar, K. Saisneha Latha, A. Bhavani Sailu, SK. Taheera, B. Madhuri. Development and Validation of RP-HPLC Method for the Determination of Pazopanib Hydrochloride (A Tyrosine Kinase Inhibitor) in Pharmaceutical Dosage Form. Research J. Pharm. and Tech 2021; 14(3):1549-1554.

30. Muhammed A. H. Aldabagh, Sahar S. Karieb, Ali N. Yassen, Saddam H. Jaber, Mohammed S. Abbas, Ali M. Jawad. Reading of Immune picture in Chronic Myeloid Leukemia in Iraqi Patients. Research J. Pharm. and Tech. 2019; 12(4):1910-1914.