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GENE EXPRESSION ANALYSIS OF EFFLUX AND INFLUX (OCT1) TRANSPORTERS IN DIFFERENT CML PHASES

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ABSTRACT

The Philadelphia (Ph) chromosome is produced by the reciprocal translocation of chromosomes 9 and 22, which is a hallmark of chronic myeloid leukaemia (CML), a clonal myeloproliferative illness. Organic cation transporter 1 (OCT-1) and organic cation/carnitine transporter 2 (OCTN2) are two membrane transporters that are necessary for the entry of imatinib into cells. Consequently, as their low expression lowers the intracellular imatinib concentration, membrane transporters have also been identified as significant factors to poor treatment response. Consequently, OCT-1, the primary influx transporter implicated in imatinib absorption in CML cells, has been identified as a critical predictor of intracellular imatinib levels attained in cells that contribute to imatinib resistance in CML patients. Investigating the gene expression of key transporters, such as P-glycoprotein (Pg-P), Multidrug Resistance Protein 1 (MRP1), Lung Resistance Protein (LRP), and Breast Cancer Resistance Protein (BCRP), during various stages of chronic myeloid leukaemia (CML) and following treatment was the aim of this study. There were five healthy controls and 120 patients with chronic myeloid leukaemia (CML). Depending on their diagnosis, the patients were grouped. Thirty patients had breast cancer, thirty had accelerated phase, thirty had blastic crisis, thirty had aphasia, thirty had chronic pain, and thirty had chronic CML. Imatinib (N=58), hydrea (N=32), or a combination of the two (N=30) were administered to the patients. Using matched blood and bone marrow samples, gene expression analysis was carried out to assess MDR marker expression throughout a range of disease stages and therapeutic approaches. The results provide insight on the mechanisms behind transporter-mediated drug resistance and might help improve CML patients' treatment regimens.

INTRODUCTION

Chronic myelogenous leukemia, often known as CML, is a kind of stem cell malignancy that arises as a consequence of the t(9;22) translocation in hematopoietic stem cells (HSCs) (Nowell & Hungerford, 1961; Rowley, 1973). This translocation leads to the transformation of human stem cells (HSCs) into leukemic stem cells (LSCs), as well as the constitutive expression of the fusion tyrosine kinase BCR-ABL1 (Heisterkamp et al., 1983). It was a significant step forward in the field of targeted treatment for chronic myelogenous leukemia (CML) when effective tyrosine kinase inhibitors (TKIs) like

imatinib were developed (O'Brien et al., 2003). However, recent evidence suggests that in approximately fifty percent to sixty percent of patients who are treated with TKI for the rest of their lives, LSCs continue to exist (minimal residual disease is maintained by a subpopulation of LSC in the bone marrow). This is a primary cause of TKI resistance (Chomel et al., 2011; Chu et al., 2011; Holyoake, Jiang, Eaves, & Eaves, 1999). Furthermore, if TKI treatment is discontinued, it can serve as a reservoir for disease recurrence (Chen & Kang, 2015; Copland et al., 2006; Jorgensen, Allan, Jordanides, Mountford, & Holyoake, 2007). Therefore, there is a considerable need to develop novel treatment techniques that target LSCs in order to enhance the probability of curing chronic myelogenous leukemia (CML).

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Alteration in ABC transporters

Drug resistance that is caused by ABC transporters is the mechanism that occurs most frequently and the one that is most clearly described in response to chemotherapy in a variety of malignancies, including leukemia. One of the most essential physiological functions of ABC transporters is to make sure that cells are protected from the numerous toxic chemicals that enter through the process of cellular absorption. It has been demonstrated that the protective mechanism provided by ABC transporter-mediated extrusion of hazardous chemicals, such as metabolic waste products, naturally occurring compounds, or pharmaceuticals, might render tumor cells resistant to the toxic effects of a variety of chemotherapeutic treatments (Rees, D. C., et al., 2009). These transporters actively efflux a number of chemotherapeutic medications from the cell in a manner that is dependent on adenosine triphosphate (ATP), and they do so through a number of efflux pumps that are positioned on the membranes of the cells. Drug efflux led to a decrease in the intracellular drug concentration, which resulted in an inadequate amount of the medication being delivered to the molecules that it was intended to treat (Higgins et al., 2001).

Drug resistance is caused by the active efflux of drug molecules from cells through ABC transporters, which results in an insufficient quantity of medication being delivered to the cells that are desired. (Rees, D. C., et al. 2009)

More than eighteen distinct transporters have been experimentally verified in chronic myelogenous leukemia (CML) and in a variety of malignancies. Among these, efflux transporters like ABCB1 (Pglycoprotein, MDR1), multidrug resistance-associated proteins (MRPs, such as ABCC1, ABCC3), or the breast cancer resistance protein (BCRP or ABCG2) and lung resistance protein (LRP) are the ones that have received the most attention from researchers. The extent to which their overexpression contributes to drug resistance has been established by a number of studies.

Furthermore, the reduction in influx transporters, such as the organic cation transporter-1 (Oct-1), has emerged as a possible mechanism responsible for ineffective medication absorption and treatment failure. This is because influx transporters are responsible for transporting ions into the cell.

According to the MDR phenotype, which was first characterized in 1976, drug resistance is associated with the overexpression of a single protein that is encoded by the ABCB1 gene. This protein is known as P-glycoprotein/MDR1, and it was discovered that it reduced drug permeability in hamster drug-resistant cells. An increase in Pg-p activity is linked to treatment failure, which can result in remission and a worse survival rate in a variety of malignancies, including leukemia. Nevertheless, the fact that the medication treatment was shown to generate MDR expression throughout the duration of treatment establishes it as the primary cause for MDR. It has been proven via a number of in-vitro studies that the increased expression of ABCB1 in sensitive CML cell lines confers resistance to treatment with imatinib. There is no consistent evidence for this resistance in vivo, despite the fact that various research have highlighted the involvement of ABCB1 in patients with chronic myelogenous leukemia to imatinib. This is the case regardless of the findings obtained in vitro. It has been observed by a number of studies that the overexpression of ABCB1transporters in advanced phase, particularly in patients who are experiencing blastic crisis, renders them unresponsive to treatment (Galimberti et al., 2005; Mahon et al., 2003; Burger et al., 2004; Mountford et al., 2004; Jordanides et al., 2006). Patients who did not obtain a full cytogenetic response were shown to have significantly higher levels of ABCB1 expression, whilst other patients were unable to detect any associations between the two.

BCRP, also known as ABCG2, is an additional significant efflux pump that is related with treatment resistance in CML. This pump is coded for via the gene ABCG2. The presence of a wide variety of substrates that have been linked to breast cancer and leukemia exists in this substance. In leukemic cells, imatinib and other tyrosine kinase inhibitors are substrates for ABCG2, which is a regulatory protein. On the other hand, it was discovered that it inhibited the expression of ABCG2, and as a result, there is some debate over whether or not it contributed to resistance (Burger et al., 2004). There have been several research that have revealed the interaction between Imatinib and ABCG2 in CML cell lines. These studies have indicated that resistance to Imatinib is produced by ABCG2, and that resistance to Imatinib may be reduced by inhibiting BCR-ABL. This suggests that BCR-ABL influences the expression of ABCG2 at a later stage of transcription. Iseri et al. (2011), Gromicho et al. (2013), and O' Hare et al. (2012) all found that the expression of MRP1 and LRP seems to have a very little impact in the development of CML resistance. Several membrane efflux transporters are overexpressed in hematopoietic stem cells for the sole purpose of protecting the cells from the genetic damage that is induced by xenobiotics and to ensure that the cells remain in a quiescent state (Zong et al., 2008; Dean et al., 2009). There are a number of chemo sensitizer or reversal compounds that have been discovered to modify resistance (Brozik et al., 2011; Shukla et al., 2012). These molecules are used to overcome any resistance that may exist. When TKIs are present in high concentrations, it has been shown that they are also capable of acting as chemo sensitizers.

Uptake transporters, including the human organic cation transporter hOCT1, have recently been anticipated to be an important treatment resistance indicator in chronic myelogenous leukemia (CML). An increased level of OCT1 was shown to be connected with Imatinib resistance, and it was discovered that OCT1 regulates the concentration of Imatinib within the cell. It was demonstrated by Crossman et al. that patients who had failed to achieve at least a minor cytogenetic response after 10 months of Imatinib therapy had a lower level of hOCT1 in their bone marrow cells compared to patients who had achieved a complete cytogenetic response (CCyR) (White et al., 2006; Crossman et al., 2005; Thomas et al., 2004; Wang et al., 2008). It has been demonstrated that patients with high OCT1 activity had the best likelihood of achieving MMR, whereas individuals with low activity require an increase in the dosage of imatinib in order to obtain optimum response (White et al., 2012).

REVIEW OF THE LITERATURE

Study by Chen, Wei-Wen, Liu, Da-Bin, Xiao, Hong-Xia, Zhou, Li-Jun, and Qu, Jia. (2022) The life-threatening hematological malignant disease known as acute myeloid leukemia (AML). The researchers confirmed that methylation is involved in

the development and progression of acute myeloid leukemia (AML). The researchers aimed to determine the mechanisms of carcinogenesis and the aberrantly methylated differentially expressed genes (DEGs) linked to AML by employing integrated bioinformatics analysis. Gene expression profiles (GSE109179, GSE142699, GSE49665, and GSE14772) and a gene methylation profile (GSE42042) were used to identify the differentially expressed genes (DEGs) that were aberrantly methylated. For the purpose of conducting functional enrichment studies on the identified genes, the Gene Ontology (GO) and Kyoto Encyclopedia of Genes and Genomes (KEGG) databases were applied. We also constructed networks of interactions between proteins. Finally, using reverse transcription-quantitative PCR on patient samples confirmed the accuracy of the DEGs. The results showed that eight upregulated genes were hypomethylated and seven downregulated genes were hypermethylated. It was discovered that the differentially expressed genes (DEGs) with differential methylation were more abundant in the GO biological process categories associated with immune response regulation. Moreover, the pathways of AML, ferroptosis, TGF-β signaling, and necroptosis were identified by the KEGG analysis as involving these DEGs.

In a recent publication by Alves et al. (2021) In the end, a cancer clone with the potential to evade therapy was chosen, and the mechanism of resistance to targeted therapies was shown to be complex and multi-factoral. It wasn't until the t(9;22)(q34;q11) mutation that cancer was shown to be associated with a genetic shift. The finding led to the development of chronic myeloid leukemia (CML). The BCR-ABL1 fusion gene came into being as a result of this translocation. The cytoplasmic chimeric BCR-ABL1 protein, encoded by this gene, had an abnormally high degree of tyrosine kinase activity. Although imatinib was effective in treating chronic myelogenous leukemia for the majority of individuals, resistance to the medicine can develop either before treatment begins or while the patient is still receiving it. It was common practice to classify CML TKI resistance pathways as either BCR-ABL1 dependent or BCR-ABL1 independent. Additionally, it was crucial for CML management that patients stick to their treatment plans and comply with all instructions. The use of mathematical modeling and computational prediction methods, along with enhanced sensitivity techniques like next-generation sequencing (NGS) and double-strand PCR, could lead to the discovery of drug resistance mechanisms and the creation of treatment strategies that are more effective in improving drug efficacy in patients with chronic myelogenous leukemia (CML).

Yoshimaru, Ryo and Minami, Yosuke (2023) As an illustration of the effectiveness of molecular targeted therapy in the management of chronic myeloid leukemia (CML), referenced tyrosine kinase inhibitors (TKIs). Some people, nevertheless, had no response to TKI therapy at all. According to the research, the most studied mechanism of TKI resistance in CML was found to be alterations in the kinase domain of BCR::ABL1. Nevertheless, it was also demonstrated that pathways unrelated to BCR::ABL1 were involved in certain cases. There are a couple of recognized processes that contribute to resistance. One is Philadelphia-associated rearrangements, which are a specific form of genomic heterogeneity that happened when the Philadelphia chromosome was developing. Mutations in genes known to be connected with cancer and rearrangements associated with Philadelphia were among these pathways. After receiving the third-generation TKI developed to fight drug resistance, the majority of patients with chronic-phase and accelerated-phase chronic myelogenous leukemia still had one or more cancer gene mutations. Survival without progression in cancer patients was found to be independently associated to cancer gene mutations and other chromosomal abnormalities.

Marjanu Elias and colleagues (2022) In the end, the BCR-ABL1 oncogene is what causes chronic myeloid leukemia, a form of blood cancer, as stated in the declaration. Even though tyrosine kinase inhibitors have been successful in treating chronic myelogenous leukemia (CML), resistance has been seen. The majority of the resistance was caused by mutations in the BCR-ABL1 gene's tyrosine kinase domain. Conversely, many cases of chronic myelogenous leukemia showed unknown resistance since the etiopathology was poorly characterized. It is probable that miRNA is a crucial component in the entire pathogenesis of chronic myelogenous leukemia (CML), making the determination of this process of the highest priority. A thorough literature assessment of microRNAs with varied levels of expression in chronic myelogenous leukemia was the goal of this research. They looked at both their target genes and those downstream as well. As far as electronic searches go, PubMed, Scopus, EBSCOhost MEDLINE, and Science Direct should be sufficient. The terms chronic myeloid leukemia, genes, and microRNAs were used in either the title or the abstract as MeSH (Medical Subject Heading) phrases. The 806 studies that were retrieved from the search were limited to clinical trials that included experimental data on the target genes of the miRNAs studied in CML cells in vitro.

According to Abdulmawjood, Bilal et al. (2021) CML is an uncommon hematological malignant proliferative disease. Its molecular hallmark was the Philadelphia chromosome (Ph). A faulty fusion gene with aberrant kinase activity came from the Ph chromosome. This caused reactive oxygen species and genomic instability, which affected the sickness. We observed that chronic myelogenous leukemia (CML) is associated with chromosomal aberrations and common altered genes in the blast phase. EGFR, TP53, and Schmidt-Ruppin A-2 proto-oncogenes regulated cell death and proliferation. Additional genes involved in cell adhesion include CTNNB1, TGF-β genes (e.g., SKIL, TGFB1, TGFB2), and TNF-α pathways (e.g., TNFA, NFKB1). The significance of microRNAs in CML was also garnering attention. Dysregulation of key miRNAs including miRNA-451 and miRNA-21 has been related to illness genesis, development, and therapy response.

Xu, Junhua et al. (2019) It was said that the majority of research on chronic myeloid leukemia (CML) had concentrated on treatment modalities, while only a small number of studies had addressed the progression of patients' illnesses after receiving pharmacological treatment. The traditional biomarkers were only able to differentiate between normal states and illness states; they were unable to identify the pre-stable condition that occurred when pharmacological therapy became effective. They offered a treatment impact detection technique for the gene expression data of CML patients that was based on dynamic network biomarkers (DNB). Using the DNB criterion, they chose a DNB that had 250 genes and created a treatment effect index (TEI) for the purpose of identifying individual

disease states. A period of one month was determined to be the pre-stable stage, which occurred before the illness status became stable. The DNB was functionally analyzed, and the results revealed that certain genes are important in determining the progression of the problems that CML patients were experiencing. The findings offered a theoretical orientation and foundation for medical professionals to follow when treating patients with chronic myelogenous leukemia (CML), and they sought to explore novel therapeutic targets for the future.

Yuan, Yunxia et al. (2020) Anemia, bleeding, fever, and infection are some of the symptoms that are associated with acute myeloid leukemia (AML), which is a malignant illness that originates from bone marrow hematopoietic stem cells and has a low survival rate. However, at that time, complete comprehension of the etiology of AML was not yet achieved. In order to shed light on the reasons behind the development of AML, the researchers utilized an integrated strategy that was founded on untargeted metabolomics and network pharmacology in their research. Through the utilization of the UHPLC-MS technology, they carried out metabolic profile research on plasma samples obtained from 14 patients and 16 healthy persons. With the use of the human metabolite database and independent sample testing, they were able to identify 23 different metabolites. This was accomplished through the use of PLS-DA, which stands for partial least squares discriminant analysis. There were primarily four metabolic pathways that were associated with AML. These pathways were fatty acid metabolism, amino acid metabolism, energy metabolism, and lipid metabolism. In the meanwhile, they established a network consisting of biomarkers, targets, pathways, and diseases, while simultaneously discovering 122 disease targets and 75 biomarker targets. In addition to this, they predicted thirty other pathways, some of which were in agreement with those found in metabolomics.

Richard Stone (2004) Participants in the course were able to analyze and discuss various CML treatment options, such as oral chemotherapy, interferon-based approaches, allogeneic stem cell transplantation, and the rationale for using imatinib as front-line therapy for chronic phase CML. They also gained an understanding of the phase III trial comparing imatinib to interferon-alfa plus Ara-C. Another option is for them to earn 1 hour of continuing medical education credit through an online test available at CME.TheOncologist.com. Imatinib mesylate, a novel molecularly targeted medicine, revolutionized the treatment of chronic myeloid leukemia (CML) and opened new avenues for the treatment of other cancers. In a targeted and powerful manner, imatinib inhibits BCR-ABL, a protein tyrosine kinase that causes chronic myeloid leukemia (CML). In a randomized, phase III study comparing imatinib to interferon-alfa and cytarabine, imatinib demonstrated the strongest evidence for its potential as a first therapy for newly diagnosed chronic-phase CML. It improved quality of life, increased disease response rates, decreased toxicity, and prolonged periods without progression. Only allogeneic stem cell transplantation proved to be an effective long-term treatment for chronic myeloid leukemia.

Chereda, Bradley, and Melo, Junia (2015) by Chronic myeloid leukemia (CML) was defined as a myeloproliferative illness originating from HSCs. In this condition, the BCR-ABL1 gene is located on the Philadelphia (Ph) chromosome, which was formed by a t(9;22) chromosomal translocation. Therefore, BCR-ABL1 was identified for the purposes of diagnosis and follow-up. Cell malignancy type 1 (CML) was produced by the BCR-ABL1 protein, namely by its constitutively active tyrosine kinase activity. Unregulated cell proliferation, myeloid hyperplasia, and 'indolent' chronic phase (CP) CML symptoms were produced by this aberrant kinase signaling, which in turn activated downstream pathways that changed the cell. A condition resembling acute leukemia, blast crisis (BC), manifested in the absence of therapy. In most cases, this advanced stage of the disease was fatal. Cellular features of chronic myeloid leukemia (CML) such as increased cell proliferation, decreased cell death, changed cell adhesion, lack of dependency on growth factors, poor genomic monitoring, and abnormal differentiation might all be explained by the existence of BCR-ABL1.

Kelesoglu, Nurdan et al. (2022) built genome-scale biological networks to combine AML transcriptome data and reporter biomolecules at the RNA, protein, and metabolite levels utilizing systems medicine and multiomics. Two separate Gene Expression Omnibus transcriptome datasets (GSE5122, GSE8970) were used. The study found novel multiomics molecular markers for AML, including miRNAs (mir-484 and miR-519d-3p), receptors (ACVR1 and PTPRG), transcription factors (PRDM14 and GATA3), and metabolites, including amino acid derivatives.

Natarajan, Aparna, Rajkumar, Thangarajan, and Kesavan, Sabitha (2019) by applying in silico approaches to repurpose existing medications, we were able to solve the problem of drug resistance. The purpose of this study was to locate compounds that may occupy the active binding site of the BCR domain and hence block the binding of Grb-2 to Y177. Through the utilization of previously existing pharmacological profiles, this computational technique aims to discover novel treatment routes for the purpose of fighting resistance in chronic myelogenous leukemia (CML). It was discovered through the analysis of differentially expressed genes from the GEO dataset that there are significant associations with a variety of biological processes.

Objective of the Study

1. To look into the analysis of efflux and influx (oct1) transporter gene expression in various cml stages.
2. To Investigating the gene expression of key transporters, during various stages of chronic myeloid leukaemia (CML) and following treatment was the aim of this study.

METHOD

For the purpose of conducting gene expression study of the efflux and inflow transporters, a total of 120 Chronic Myelogenous Leukemia (CML) patients with matched blood and bone marrow samples were used. Those who were diagnosed with the condition (N=30), those who were diagnosed with chronic pain (N=30), those who were diagnosed with aphasia (N=30), those who were diagnosed with breast cancer (N=30), and those who were healthy controls (five participants) were all included in the study. A further division of the patient cohort was made according to the treatment that each individual patient received. Imatinib was given to 58 patients out of the

total, whereas Hydrea was administered to 32 patients, and a combination of the two was administered to 30 patients.

We evaluated the fold change expression levels of Pg-P, BCRP, LRP, and MRP1 in patients who were experiencing Chronic, Accelerated, and Blastic crises. This was done so that we could analyze the multidrug resistance markers. In addition, we have investigated the levels of expression in blood and bone marrow samples extracted from patients with Ph+ chronic myelogenous leukemia, as well as in a variety of therapy scenarios.

Analysis

Fold Change Expression in Different Phases of CML

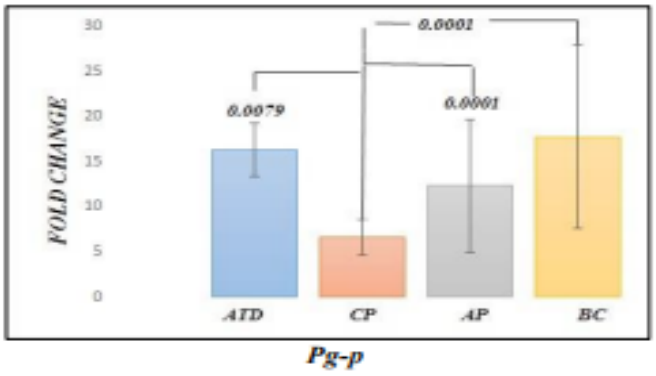
successive stage of the evolution of the illness, including the chronic phase, the accelerated phase, and the blastic crisis. The findings of the study were as follows: [CP vs AP, p< 0.001; CP versus BC, p< 0.001), AP versus BC, p< 0.001) respectively. to put it another way.

Fold Change Expression In Different Treatment Conditioned

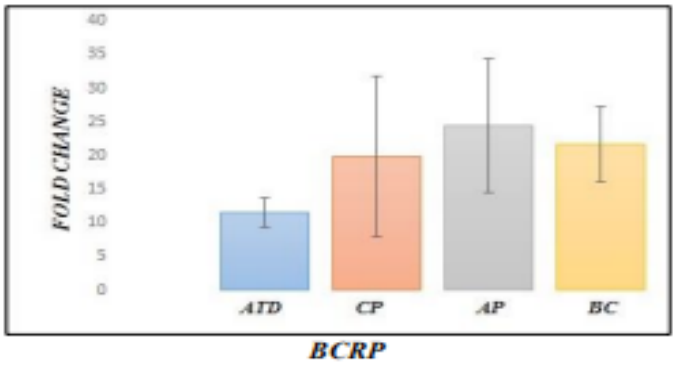
In addition, patients who were given one of three treatment conditions—hydrea alone, imatinib alone, or a combination of the two—were examined further for the expression of MDR genes. When compared to patients who just received Imatinib and Hydrea, those who received Imatinib and Hydrea together

Table 1. Expression of Multidrug resistance gene in CML Phases

Phases	PG-P (Mean ±SE)	BCRP (Mean ±SE)	LRP (Mean ±SE)	MRP1 (Mean ±SE)
ATD	16.3281±2.90246	11.51±2.20	115.698±64.698	19.9456±9.987
CP	6.6444±1.99490	19.83±11.89	84.79±78.39	8.9317±5.789
AP	12.3072±7.39932	24.42±9.86	58.16±31.16	7.7563±4.75656
BC	17.7644±10.17179	21.65±5.64	178.06±55.34	38.2720±28.17312
	p-value	p-value	p-value	p-value
ATD vs CP	0.0079	0.0432	0.1012	0.0001
ATD vs AP	0.6149	0.0658	0.0001	0.0001
ATD vs BC	0.8925	0.045	0.0002	0.0014
CP vs AP	0.0001	0.5274	0.0892	0.3937
CP vs BC	0.0001	0.7178	0.0001	0.0001
AP vs BC	0.0693	0.8039	0.0001	0.0001



Pg-p



BCRP

As evaluated by fold change, the expression of Pg-P was shown to be significantly greater in the blastic crisis when compared to the chronic phase and the accelerated phase (CP vs AP, P 0.0001 and CP versus BC, P 0.0001, respectively). This was seen in comparison to the chronic phase and the accelerated phase. Individuals who are experiencing chronic, accelerated, or blastic crises, as well as those who are experiencing accelerated or blastic crises, do not differ substantially from patients who were not receiving treatment. As far as the BCRP is concerned, there have been no noticeable alterations seen in the latter stages of the illness. In addition, the MRP1 level had a significant increase as the diseases progressed to the stage of blastic crisis [CP vs BC, p< 0.0001; AP against BC, p< 0.0001]. The expression of LRP also increased significantly with each

showed a much higher fold change expression level of Pg-P and BCRP. However, it is worth noting that there are notable differences seen in the comparisons of Imatinib and Hydrea (p<0.0001), Imatinib and Hydrea in contrast to each other (p<0.0001), and Hydrea and Imatinib+Hydrea (p<0.0001). Hydrea patients demonstrated a higher fold change expression for MRP1 and LRP when compared to patients who were treated with imatinib or patients who received a combination of imatinib and hydrea. A considerably higher fold change expression was only seen in the case of MRP1, with a statistical significance level of p<0.0001. It was not possible to find a statistically significant difference between any of the three treatments when analyzing LRP.

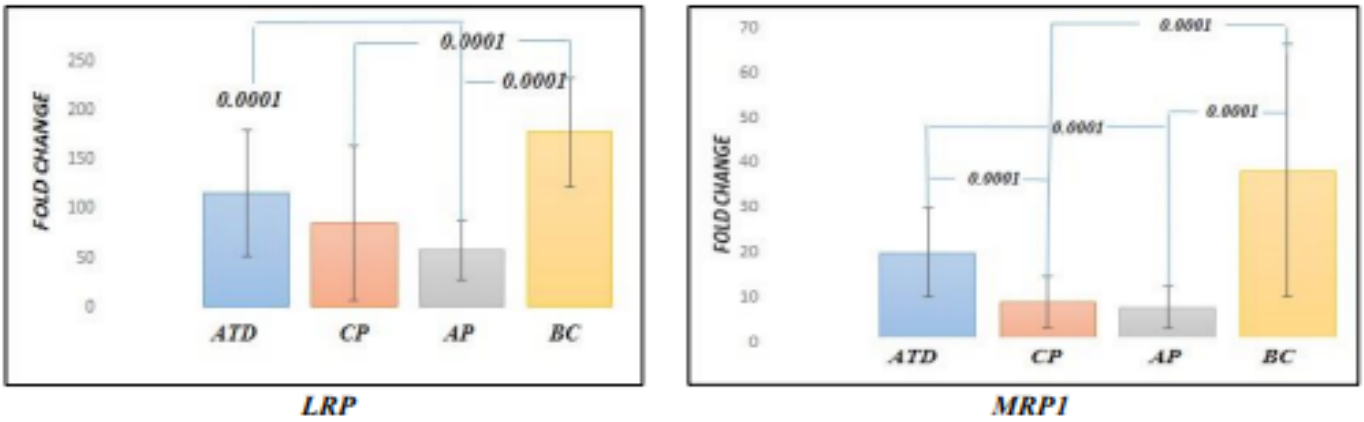


Figure 1. Represents the fold change expression of Pg- p, BCRP, LRP and MRP1 in different phases of CML

Table 2. Differential Expression of Multidrug Resistance Gene in Different Treatment Conditions

Treatments	PG-P (Mean ±SE)	BCRP (Mean ±SE)	LRP (Mean ±SE)	MRP1 (Mean ±SE)
Imatinib	3.5080±0.57398	16.68±2.34	47.89±26.75	3.9378±1.89
Hydrea	18.2893±3.5435	12.82±3.50	120.84±50.24	32.7022±18.65
Imatinib+Hydrea	27.1840±7.1717	40.31±12.60	78.976±22.67	17.590±7.37
	P-Value	P-Value	P-Value	P-Value
Imatinib vs Hydrea	0.0001	0.001	0.0001	0.0001
Imatinib+ Hydrea vs Hydrea	0.0001	0.001	0.0001	0.0001
Imatinib+ Hydrea vs Imatinib	0.0001	0.001	0.0001	0.0001

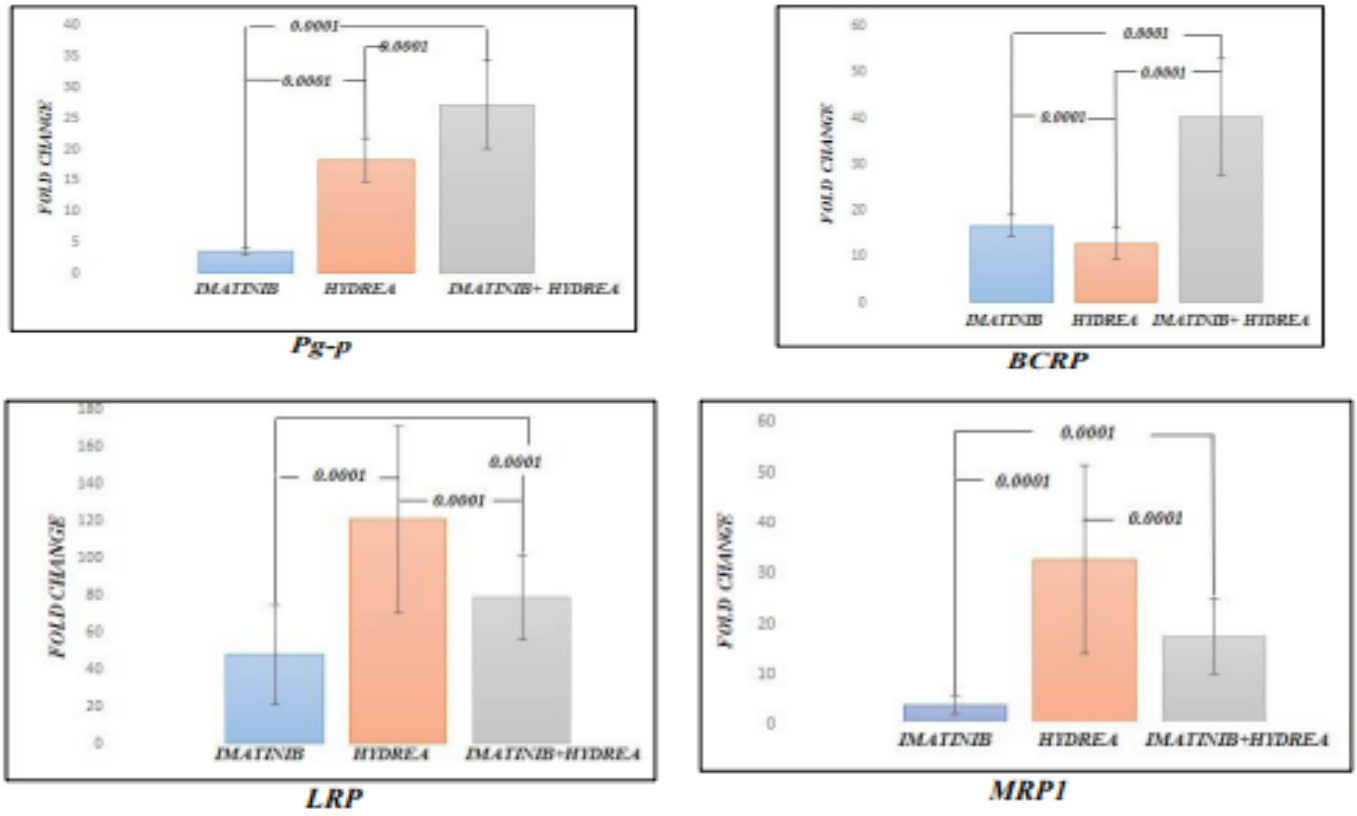


Figure 2. Represents the fold change expression of Pg-p, BCRP, LRP and MRP1 in different treatment conditions

Fold Change Expression between Bone marrow and Blood samples

Assessment of Multidrug Resistance Markers: Influx transporter (OCT-1)

Table 3. Differential Expression of MDR in Bone marrow and Blood Samples

Phases	MDR GENES	Mean ±SE (BM)	Mean ± SE (BLOOD)	p-VALUE (BM vs BLOOD)
CP	PG-P	2.0355±0.34069	10.7986±2.35709	0.0015
	BCRP	1.5088± 0.37902	22.8790±3.99650	0.0001
	LRP	182.99± 15.01	0.086±0.0265	0.0001
	MRP1	17.2416±2.24	0.6218±0.152	0.0001
AP	PG-P	0.7650±0.15948	15.2315±5.95783	0.0167
	BCRP	1.3920±0.71917	34.0198±13.10752	0.0143
	LRP	108.06±28.17	14.11±1.44	0.0012
	MRP1	12.0090±1.62	3.5036±0.66	0.0001
BC	PG-P	7.7581± 4.21815	31.9067±7.26651	0.0048
	BCRP	2.6188±0.31253	33.3585±7.46661	0.0001
	LRP	205.54± 6.76	90.19±7.48	0.0001
	MRP1	66.6345±9.99	9.9095±1.88	0.0001

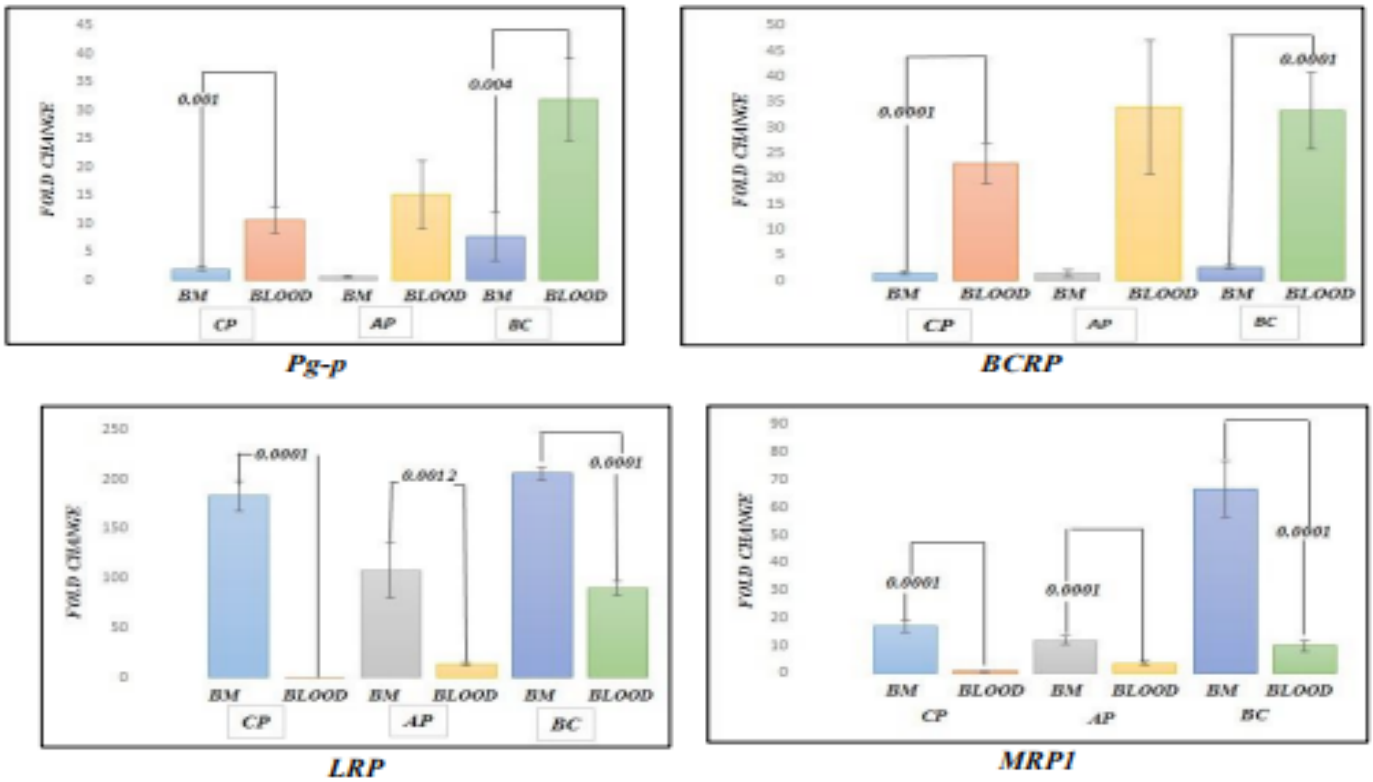


Figure 3. Represents the fold change expression of Pg- p, BCRP in Bone marrow and Blood samples

Figure 3.1. Represents the fold change expression of LRP and MRP1 Bone marrow and Blood samples In addition, we have used samples taken from a variety of sources in order to investigate the ways in which the expression of MDR proteins has changed during the different phases of cerebral malignant leukemia. During Chronic, Accelerated, and Blastic crises, we discovered that the fold change expression of Pg-P and BCRP was higher in blood samples than it was in bone marrow samples. This was the case regardless of treatment. It was observed that the link between MRP1 and LRP was the reverse. During the transition from the chronic phase to the blastic phase, bone marrow and blood samples exhibit fold changes that are much larger ($p< 0.0001$).

We assessed the fold change in OCT-1 levels in patients who were experiencing Chronic, Accelerated, and Blastic crises so that we could estimate the amount of influx transporter expression. In addition, we have investigated the levels of expression in blood and bone marrow samples extracted from patients with Ph+ chronic myelogenous leukemia, as well as in a variety of therapy scenarios.

Fold Change Expression in Different Phases of CML and in different treatment Conditioned

When the expression of the OCT-1 transporter gene was evaluated throughout the several phases of chronic myeloid leukemia, it was found that the expression of the gene was

Table 4. Expression of OCT-1 transporter In CML Phases and different treatment conditioned

Phases	Oct-1 Mean ±SE	Treatments	Oct-1 Mean ±SE
ATD	30.025 ±7.50625	Imatinib	13.10±2.882066
CP	32.0248±5.444216	Hydrea	30.02± 7.50625
AP	12.6300±2.7786	Imatinib+Hydrea	30.21± 7.252127
BC	17.3700±2.9529		
	P-Value		P-Value
ATD vs CP	0.8300	Imatinib vs Hydrea	0.0135
ATD vs AP	0.0339	Imatinib+ Hydrea vs Hydrea	0.9855
ATD vs BC	0.1221	Imatinib+ Hydrea vs Imatinib	0.0114
CP vs AP	0.0024		
CP vs BC	0.0213		
AP vs BC	0.2472		

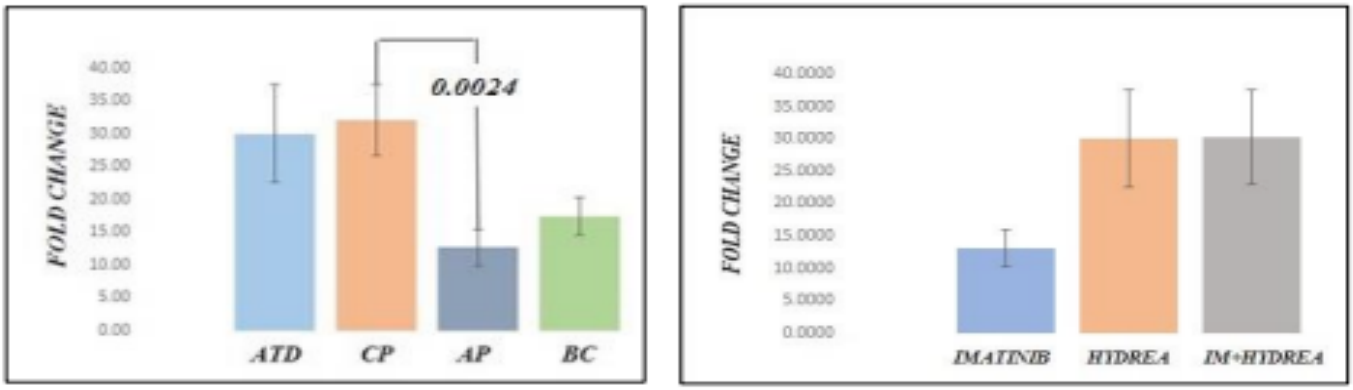


Figure 4. Differential Expression of OCT- 1 indifferent CML phases. Figure 4(a). Differential Expression of OCT-1 inin different treatment conditions

dramatically downregulated as the disease progressed to blastic crisis [CP vs. AP, p=0.0036]. There has been no visible difference between AP and BC, despite the fact that there was. OCT-1 levels were shown to be downregulated in patients taking Imatinib alone compared to those getting Hydrea and Imatinib+Hydrea under a variety of situations. This was the case despite the fact that there was no significant difference between Hydrea and Imatinib+Hydrea. This lends credence to the idea that hydrea is involved in the process of inducing OCT-1.

Fold Change Expression between Bone marrow and Blood Samples

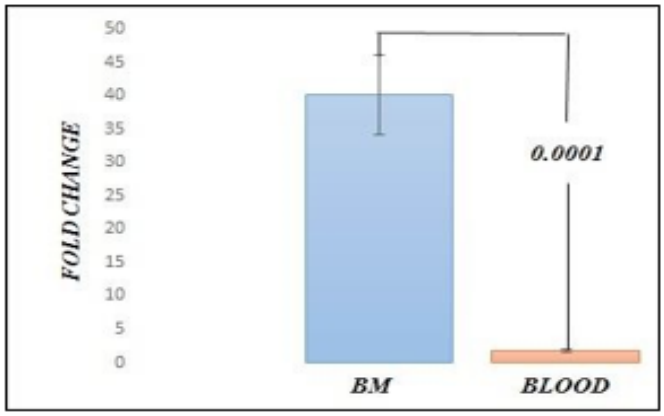
After doing a comparison of the expression of Oct-1 in different sample sources, it was shown that the expression was considerably greater in bone marrow samples compared to blood samples ($p<0.0001$). In a similar vein, when comparing the expression of Oct-1 in various stages of the same sample sources, bone marrow samples consistently performed better than blood samples.

CONCLUSION

This study underscores the significance of efflux and inflow transporters in the progression of chronic myeloid leukaemia (CML) and therapeutic responsiveness. Significant variations in the expression of Pg-P, BCRP, LRP, and MRP1 were seen throughout different phases of CML, indicating that these proteins may contribute to treatment resistance. Furthermore, differences in transporter expression across blood and bone marrow samples suggest distinct regulation mechanisms in various biological compartments. The findings underscore the need for personalised therapeutic approaches targeting MDR transporters to enhance treatment outcomes for individuals with CML. Future research should focus on developing targeted inhibitors or combination therapies to address resistance and enhance the efficacy of current treatment protocols.

Table 5. Differential Expression of OCT-1 in BM and Blood Samples

Phases		Mean ±SE (BM)	Mean ± SE (BLOOD)	P-VALUE (BM vs. BLOOD)
CP	OCT1	28.59± 24.86	2.13± 0.69	0.249
AP		61.92 ±15.86	1.99± 0.41	0.0001
BC		29.51 ±6.99	1.18± 0.31	0.023
Overall expression		40.11± 6.01	1.77± 0.29	0.0001



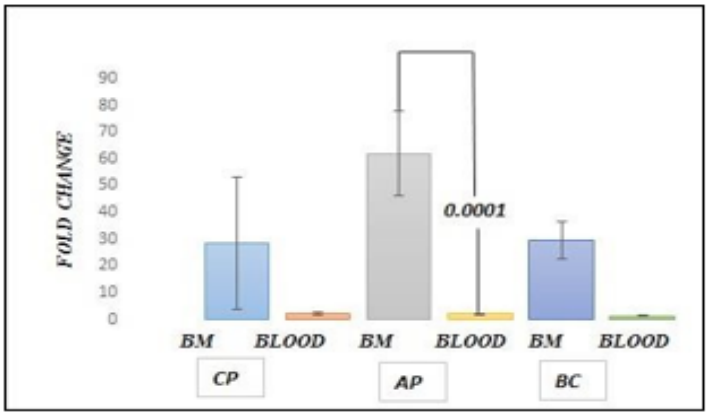


Figure 5. Overall expression of OCT-1 in BM and Blood Samples Figure 6. Differential Expression of OCT- 1 in BM and Blood samples of CML Phases

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