Identification of MRP1 and its role in complete remission (CR) after induction therapy in Acute Myeloid Leukemia patients.

SABA KAMIL (Saba.kamil@duhs.edu.pk)
Dow University of Health Sciences
SHAHEEN KOUSER
Dow University of Health Sciences
NADIA NAEEM
Dow University of Health Sciences
WAQAS FARROQUI
Dow University of Health Sciences
GHULAM HAIDER
Jinnah Postgraduate Medical Center
Farrukh Ali KHAN
Dow University of Health Sciences
SHAHEEN SHARAFAT
Liaquat National Hospital
NOOR KAMIL
Salim Habib University

Article

Keywords: MRP1, Remission, FLT3, NPM1, Cytogenetics

Posted Date: September 2nd, 2022

DOI: https://doi.org/10.21203/rs.3.rs-2002513/v1

Abstract

Adenosine triphosphate (ATP) binding transporters are one of the chief reason behind drug resistance. There are forty nine adenosine triphosphate binding cassette (ABC) transporters. Some of them are Multidrug resistance associated protein-1 (MRP 1), Breast resistance cancer protein (BCRP), and P glycoprotein (P-gp). Their expression in the cell causes expel out of drugs from the cell. Therefore, the patient is incapable of achieving remission or may relapse.

Methodology: Peripheral blood samples of 40 patients with denovo AML were taken in this study. QRT PCR and ELISA was performed to evaluate the MRP 1 gene and MRP 1 protein expression respectively. A relationship was analyzed between MRP 1 expression and complete remission.

Results: Out of 40 patients, males were predominant i.e., 55 percent in the current research. The frequency of acute myeloid leukemia was the highest in the age group of 25–39 years both in males and females. Between MPR 1 gene expression and complete remission, clinical relevance was observed in this study, 69.2 percent of patients with high gene expression failed to attain complete remission (P value > 0.05) whereas results of MRP 1 protein analysis was statistically nonsignificant. Moreover, other parameters such as FLT3, NPM1, and cytogenetics indicated no relationship with MRP 1.

Conclusion: This study provides a basis to further evaluate the role of ABC transporters for future researches. However, larger sample would be required to validate the results.

Introduction

Malignancy is one of the most common reasons for mortality worldwide. According to the World Health Organization statistics, around 13.1 million deaths can be anticipated by 2030 owing to malignancies (1). Hematological malignancies are the most lethal malignancy consisting of 4% of all cancers. Numerous researches have proposed that it is considered the most common cause of death below 40 years age in males, and around half of all new malignancies in females are associated with blood cancer. Acute myeloid Leukemia characterizes as mixed malignancy categorized by clonal multiplication and compromised of differentiation of myeloid precursors with varied outcomes. Even though improvements in concepts of the molecular diversity and pathogenesis of AML, and slight advancement in the conventional therapy for AML over the past forty years but treatment failure, advanced disease and narrow treatment choices remain significant hurdles for AML patients. Drug resistance can also cause failure in induction or relapse (2). Some recognized causes of drug resistance include specific proteins and enzymes, variations of miRNAs, and atypical activation of specific signal pathways involved in drug resistance. One of the major reason of treatment failure is drug efflux by some transporters present on the cell membrane. Some transporters are substrate-specific for certain anticancer drugs, specifically cytarabine and daunorubicin. Several drug transporters have been well researched, like P glycoprotein (P-gp/MDR1/ABCB1), which belongs to the ATP-Binding Cassette (ABC) superfamily, multidrug resistance protein 1 (MRP1/ABCC1) and breast cancer resistant protein (BCRP/MXR/ABCP/ABCG2) (3) The human

multidrug resistance-associated protein 1 (MRP1) is a member of the ATP-binding cassette (ABC) transporter superfamily and is encoded by the ABCC1 gene on chromosome 16p13.1 (4). MRP1 is a single polypeptide chain consisting of three membrane spanning domains, two cytosolic nucleotide-binding domains (NBD1 and NBD2), and the N terminal of unidentified function as represent in Fig. 1. When substrate binds to transmembrane domain, drug enters into the cell. Nucleotide binding domain dimerizes causes TMDs facing outwards causes efflux of drug outward (Fig. 2). MRP 1/ ABCC1 is responsible for the efflux of necessary anticancer drugs, for instance, Vinca alkaloid, Anthracycline, and Methotrexate (5).

Objectives of the study

- To ascertain the expression of the MRP1 gene in AML patients
- To determine the relationship between MRP1 gene expression and response to remission induction in AML patients
- To estimate the MRP1 protein expression in prechemotherapy patients regarding remission induction in AML patients

Materials And Methods

The study conducted was a cross-sectional longitudinal analysis. The ethical approval of this study was conferred by the Institutional Review Board of Dow University of Health Sciences through letter reference no IRB-1663/DUHS/Approval/2020 dated June 8, 2020. The peripheral blood samples (n=40) of diagnosed AML patients before chemotherapy were collected from the bone marrow transplant unit of Ojha (Dow University of Health Sciences) and Jinnah Postgraduate Medical Center (JPMC). Informed consent obtained from all participants before taking the blood samples. The experiment was carried out in Dow Diagnostic Research and Reference Laboratory (DDRL) at the Dow Research Institute of Biotechnology and Biosciences (DRIBBS) Karachi, Pakistan. The duration of this study was 15 months, starting from July 2020 to September 2021, after approval from the Ethical Committee, Institutional Review Board (IRB on June 8, 2020), and Board of Advanced Studies and Research (BASR on September 5, 2020). AML patients both male and female ranging from 16 to 60 years on same treatment protocol were included in this study. Patients with APL (AML-M3) and patients who expired during induction chemotherapy were exclude out from this study. Using Statistical Package for Social Sciences (SPSS) version 21, the data variables were assessed. Descriptive analysis was carried out to generate frequency distributions. Categorical data were analyzed by using chi-square. An inter-class correlation was done to check the agreement between the two techniques either results of qRT PCR and ELISA is comparable or not.

Treatment protocol and complete remission

AML patients received 3+7 regimen (3 d of an IV anthracycline daunorubicin at least 60 mg/m^2 7 d of continuous infusion cytarabine (100-200 mg/m2) were assessed for complete remission after induction

therapy. Complete remission is explained by blast cells lower than 5 percent in bone marrow with absence of Auer rods and extramedullary disease and return of peripheral blood report to normal.

RNA Extraction and Real-time quantitative reverse transcription polymerase chain reaction (qRT PCR)

The mRNA level of multidrug resistance gene MRP1 were analyzed by qRT PCR. Isolation of total RNA was done by using Nucleospin RNA blood kit according to manufactures guidelines. Then RNA was reverse transcribed according to the instruction of Revert Aid First Strand cDNA Synthesis Thermoscientific Kit. The final step was qRT PCR by following the manufacturers protocol (Bright Green 2X qPCR MasterMix- Low ROX. Cat no: MasterMix-LR). Reaction mixture 10 microliter was prepared by adding master mix 5 microliter, primers 0.5 microliter, cDNA 2 microliter, nuclease free water 2.5 microliter. Denaturation step (95 °C for 3 sec) followed by primer annealing (60° C for 30 seconds). The expression level of target gene was calculated by normalizing it to a housekeeping gene beta actin. The relative gene expression levels were calculated by the 2−ΔΔCT method then two-fold change was calculated. Determination of MRP 1 mRNA were done in triplicate.

Primers

The sequence of primers for MRP 1 Forward- CAGCCTACTGCCTCGGATCT Reverse- ACTGCAGCCCCAAGGAATG. B ACTIN Forward- TGGGCATGGGTCAGAAGGAT Reverse- AGGTGTGGTGCCAGATTTTCTC

Protein (MRP 1) expression analysis by ELISA

The serum was separated out in two aliquots for duplicate reactions and stored at -80 °C till further process. Firstly Standard sample solution was made again with 1 ml of standard diluent. The concentration of standard in stock solution was 10ng/ml. Standard diluent of 0.5ml were made in 7 tubes and double serial dilution was prepared. Each tube was comprehensively mixed. The Tubes were arranged as 10ng/ml, 5ng/ml, 2.5ng/ml, 1.25ng/ml, 0.625ng/ml, 0.312ng/ml, 0. 156ng/ml. The wells were assigned as standard, blanks and samples. Diluted standard of 100 µl was added in each well. The plate was incubated for 1 hour at 37°C. About100 µl of Detection reagent was added and incubated at 37°celsius for one hour. The solution was aspirated and washed thrice with 350 µl wash solution. After the last wash, any remaining wash buffer was discarded by aspirating and the plate was inverted on an absorbent paper. Then 100 µl of detection reagent B was added and the plate was once again covered with sealer and incubated for 30 minutes at 37°C. The solution was washed 5 times with wash solution. 90 µl of TMB substrate was added in each well and incubated for 20 minutes at 37°C. 50 µl of Stop solution was added to each well. The Optical density was recorded at 450nm. The average was taken for each duplicate reading for standards and samples and the blank was subtracted.

Result

40 patients of denovo AML were included in this study, 20 patients achieved remission, 13 patients has high expression of MRP 1 gene and 27 patients has low expression. Demographic analysis shown in Figs. 3 and 4. Table 1 shows 4 (30.8%) patients who achieve remission had high expression of gene while 9 (69.2%) of the patients fail to achieve remission had high expression of MRP 1. Statistical evaluation shown non significant p value which might be due to smaller sample size. Table 2 shows relationship between MRP 1 proteins with complete remission, out of 40 patients 5(38.5%) had high expression of MRP 1 protein with no remission. Statistical results were non-significant. Association between FLT3 and MRP 1 was analyzed and results were statistically non significant as presented in table We investigated whether there is an association between cytogenetics with MRP 1 gene expression in table and we found no association between them. We further investigated whether the association between NPM1 and MRP 1 exists, results showed non significant P value in Table 1.

Table 1
Number of patients with and without remission in relation to **MRP1** gene in AML patients

MRP1	Achieve Remission		P-value
*G*ene	**Yes**	**No**	
High expression	**4 (30.8%)**	9 (69.2%)	0.091^
Low expression	16 (59.3%)	11 (40.7%)	

Table 2
Number of patients with and without remission in relation to MRP1 protein in AML patient

MRP1 Protein	Achieve Remission		P-value
	Yes	**No**	
High expression	11 (40.7%)	5 (38.5%)	0.890^
Low expression	16 (59.3%)	8 (61.5%)	

Intraobserver Reliability

We found no agreement of MRP 1 when observed through two techniques (PCR and ELISA) by applying intraclass correlation (ICC = 0).

Discussion

Effective treatment in AML remains an unsolved question. Conventional methods like Cytarabine, Daunorubicin, or Idarubicin, though effective, cause chemotherapy resistance which is a prevailing

problem that brings about resistance and ultimately death. Going into a novel prognostic marker can be effective for personalized treatment in leukemia patients (6, 7). Hitherto, a considerable number of AML patients did not attain complete remission, several patients responded poorly and relapsed later. Though drug resistance remains an area of interest for researchers, further researches need to be conducted. Various methods have been developed regarding drug resistance such as drug resistance associated proteins like Multidrug resistant protein (MDR), Lung related protein (LRP), MRP 1, Breast cancer resistant protein (BCRP), etc. Some enzymes like Glutathione S-transferases (GST), Protein kinase C (PKC), etc. also play a vital role. Gene alteration plays a significant role in drug resistance (FLT3, RAS family, IDH, ASXL1). Several inhibitors are on clinical trials to restrain drug resistance (8). The contribution of efflux transporters like ABC transporters is of primary concern for drug resistance as the chemotherapeutic drug influx is imperious for successful treatment (9). Even though extensive studies have been done, the role of ABC transporters is so far not comprehensible. ABC transporters are one of the largest families of transmembrane proteins, found in every living organism and play a primary role in drug efflux, which is the most usual cause of drug resistance. Many of the ABC transporters have been investigated in various malignancies like prostate (10), neuroblastoma (11), blood malignancies (9), etc. Several researches manifested coexpression between ABC transporters. Coexpression, considered one of the poor prognostic markers, is compared with those who expresses one efflux transporter (ABC) (12–17). In our population, a small number of drug resistance transporters have been examined. From this perspective, the current research was designed to explore one of the ABC transporters, MRP 1, in AML patients. MRP 1 protein in AML patients in our population has not been investigated yet, but it was analyzed by ELISA.

Demographic analysis revealed that males are more affected than females (Fig. 3) in this study. This finding is consistent with previous studies (7, 9). As long as the age is concerned, the mean age was found to be 33.15 ± 10.63. Most of the patients were between 25 to 39 years of age (Fig. 4)This finding is in line with other studies that reported more patients were enrolled between 15 to 40 years of age (9). The reason for the predominance of young adult males in AML might be because of obesity, poor dietary habits, or occupational hazards like ionizing radiation, tobacco smoking, and people belonging to rural areas working in agriculture fields, or animal farming (18, 19). Nearly 80% of younger AML patients reached remission after induction therapy and a majority of them relapsed with resistance to the current treatment method. Even in patients treated with aggressive therapy, the 5 year survival rate is less than 35% (20–22). Some of the drug efflux transporters corresponding to age have been analyzed such as MDR1 expression. The efflux of the drug grew with age from 17% in patients less than 35 years old to 39% in patients above 50 years. In opposition to MDR1, expression of MRP 1 decreased with the age of the patients. Likewise, expression of BCRP was high in above 60 years patients (ABC/ efflux transporter) (22–24). According to the current study, the expression of MRP1 increased (70.6%) with the age between 25 to 39 years (70.6%) contrary to patients less than 25 years (27.3%).

This study found that there is a upregulation of MRP 1 gene in patients who didn’t reach remission (69.2%) as shown in (Table 1). Maria Paprocka1 et al also reported overexpression (86%) of MRP 1 in patients who didn’t reach remission (7). Though, some other studies showed that MRP 1 had no significance to anticipate treatment response, has no prognostic value, and its relationship with remission

is somehow contentious (25–29). On the other hand, Antonella Maria Salvia, et al. noticed upregulation of ABCC1/ MRP1 in relapsed and no remission groups. They also asserted that failure in chemotherapeutic response can be due to MDR 1 gene (one of the ABC transporter) which was related to poor prognosis (30). There are 49 ATP-binding cassette (ABC) transporters express on multiple cells of the body and several researches have revealed the role of multidrug resistance genes in several carcinomas. One previous research concerning multidrug resistance was conducted in Russia in 2019 which presented its results about one of the multidrug resistance genes MDR 1 in primary AML patients, in which MDR 1 moderately corresponded to poor therapy response and resistance to cytarabine, and strongly corresponded to resistance with daunorubicin (31). In 2019, Huang Y et al examined ABCB1, ABCB4, ABCC1, ABCC4, and ABCG2 gene expression in 96 AML patients and found out that patients with no complete remission had a higher level of multidrug resistance protein. They also established that failure to efflux transport inhibitor therapy could be due to the existence of more than one transporter (12, 32).

Literature search suggested that acute myeloid leukemia has diverse entities observed by diverse pathophysiologic, clinical, cytogenetic, and molecular profiles that benefit from customized treatments and have different responses and results. Based upon cytogenetics and molecular profile, patients are categorized as favorable, intermediate, and unfavorable risk groups as stated earlier. FMS-like tyrosine kinase 3 (FLT3) plays a major role in cell proliferation and the survival of hematopoietic progenitor cells. It mutates frequently in AML patients accounting for 25 to 30% (33). There is a poor risk of FLT3 mutation with normal cytogenetics. NPM1 is another mutation found in AML, and it occurs in 45–64% of the AML cases. With good cytogenetics, patients with NPM1 mutation have a good prognosis, but when it coexists with FLT3/ ITD, it shows a poor prognosis (34–36). Hirsch and his co-workers investigated the relation between multiple prognostic specifications like age, FLT3, NPM1, CEBPA, and the role of ABC transporters as an autonomous prognostic factor in adult AML patients with favorable karyotyping (12, 37). With respect to previous researches, the relationship of FLT3, NPM1, and cytogenetics with our gene of interest i.e. MRP 1 in this study was analyzed.

As far as the relationship between FLT3 and MRP 1 expression is concerned, it was found that FLT3 positive patients showed overexpression of MRP1 but our results were statistically insignificant (Table 3) which is in accordance with the analysis of Salvia AM and his colleagues who reported overexpression of ABCC1/MRP1 and ABCC6 (one of the efflux transporter) in FLT3 positive AML patients (28).

Table 3
Association between FLT3 mutation and **MRP 1** gene expression

MRP 1 gene	FLT3 Mutation		P-value
	Positive	**Negative**	
High Expression	4 (66.7%)	14 (43.8%)	0.138^
Low Expression	2 (33.3%)	18 (56.3%)	

Clinically, NPM1 mutations have a significant impact on prognosis in acute myeloid leukemia patients. It has been recorded that patients with the NPM1 mutation have a favorable prognosis and notable complete remission (CR) after chemotherapy compared to non-mutated patients (38). About NPM1 mutation and MRP 1, no significant relation was found in the research Table 4 which is in line with previous studies. As far as the association between MRP 1 and karyotyping is a matter of concern, the current study didn't find any association between them Table 5 which is in agreement with previous studies (13, 37, 38). However, some studies reported that the deletion of MRP 1 in inv (16) karyotype was connected with good outcomes in AML patients (13, 30, 39).

Table 4
Number of the patients with NPM1 mutation in association with MRP 1 gene expression

MRP 1 Gene	NPM1		P value
	Positive	**Negative**	
High expression	8 (40.0%)	7(38.9%)	0 .944^
Low expression	12(60%)	11 (61.1%)	

Table 5
Association between Favorable and unfavorable karyotyping with MRP 1 gene

MRP 1 Gene	Karyotyping		P value
	Favorable	**Unfavorable**	
High expression	**7 (46.7%)**	**12 (50%)**	**0 .839^**
Low expression	**8 (53.3%)**	**12 (50%)**	

^ Chi square Test; P value < 0.05 considered as statistically significant

Previous researches have suggested that efflux transporters can be regarded as independent prognostic markers in addition to FLT3, NPM1 mutation, and cytogenetics (37, 40).

Strength Of The Study

Patients recruited for this study have received the same type of treatment protocols and were pursued prospectively for the assessment of the remission status to reduce the heterogeneity of the data. MRP 1 was never done in Pakistan before.

Conclusion

Based on the similar previous studies multidrug resistance is one of the major cause of treatment failure in AML patients but we haven't found statistical significance in this study. Though P value was near to

significance i.e. 0.09 therefore, it can be concluded that comprehensive multicenter studies with increase in the sample size are prerequisite to validate the findings of this study. This study might be helpful for oncologist and researches to choose the better treatment options after confirmation of the results.

Declarations

Ethics approval and consent to participate

All procedures performed in studies involving human participants were under the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

Consent for publication

All authors unanimously consented to submit manuscript in scientific reports for publication.

Availability of data and materials

The datasets supporting the conclusions of this article cannot be shared for confidentiality reasons of participant institutions. However, correspondence author should be contacted if someone wants to request the data from this study.

Conflict of interest

All authors unanimously declare that they do not have any conflict of interest.

Funding

None

Authors' contributions

KS designed the study; wrote the manuscript and interpretation of the data; S K and FA critical revision of the manuscript for important intellectual content; N N experimental work and data interpretation; W F Statistics and data analysis; G H helped in sample collection; NK given final approval of the version to be published. All authors provided critical feedback and helped shape the research, analysis, and manuscript

Acknowledgement

I would like to express my deepest gratitude my supervisor Dr Shaheen Sharafat for her constant guidance and support, staff Tabussam for her help in collection of samples. I would like to acknowledge and give my warmest thanks to Dr Nadia Naeem who made this work possible.

References

1. Organization WH. World health statistics 2010: World Health Organization; 2010.
2. Degos L. John Hughes Bennett, Rudolph Virchow… and Alfred Donne: the first description of leukemia. The hematology journal: the official journal of the European Haematology Association. 2001;2(1):1.
3. Kunadt D, Dransfeld C, Dill C, Schmiedgen M, Kramer M, Altmann H, et al. Multidrug-related protein 1 (MRP1) polymorphisms rs129081, rs212090, and rs212091 predict survival in normal karyotype acute myeloid leukemia. Annals of hematology. 2020;99(9):2173–80.
4. Megias-Vericat JE, Martinez-Cuadron D, Herrero MJ, Rodriguez-Veiga R, Solana-Altabella A, Boluda B, et al. Impact of combinations of single-nucleotide polymorphisms of anthracycline transporter genes upon the efficacy and toxicity of induction chemotherapy in acute myeloid leukemia. Leukemia & Lymphoma. 2021;62(3):659–68.
5. Johnson ZL, Chen J. ATP binding enables substrate release from multidrug resistance protein 1. Cell. 2018;172(1–2):81–9. e10.
6. Chen B, Lee JB, Kang H, Minden MD, Zhang L. Targeting chemotherapy-resistant leukemia by combining DNT cellular therapy with conventional chemotherapy. Journal of Experimental & Clinical Cancer Research. 2018;37(1):1–11.
7. Paprocka M, Bielawska-Pohl A, Rossowska J, Krawczenko A, Duś D, Kiełbiński M, et al. MRP1 protein expression in leukemic stem cells as a negative prognostic marker in acute myeloid leukemia patients. European journal of haematology. 2017;99(5):415–22.
8. Zhang J, Gu Y, Chen B. Mechanisms of drug resistance in acute myeloid leukemia. OncoTargets and therapy. 2019;12:1937.
9. Kulsoom B, Shamsi TS, Afsar NA. Lung resistance-related protein (LRP) predicts favorable therapeutic outcome in Acute Myeloid Leukemia. Scientific reports. 2019;9(1):1–11.
10. Emmanouilidi A, Casari I, Gokcen Akkaya B, Maffucci T, Furic L, Guffanti F, et al. Inhibition of the lysophosphatidylinositol transporter ABCC1 reduces prostate cancer cell growth and sensitizes to chemotherapy. Cancers. 2020;12(8):2022.
11. Muriithi W, Macharia LW, Heming CP, Echevarria JL, Nyachieo A, Niemeyer Filho P, et al. ABC transporters and the hallmarks of cancer: roles in cancer aggressiveness beyond multidrug resistance. Cancer Biology & Medicine. 2020;17(2):253.
12. da Cunha Vasconcelos F, de Souza PS, Hancio T, de Faria FCC, Maia RC. Update on drug transporter proteins in acute myeloid leukemia: Pathological implication and clinical setting. Critical reviews in oncology/hematology. 2021:103281.
13. Liu B, Li L-J, Gong X, Zhang W, Zhang H, Zhao L. Co-expression of ATP binding cassette transporters is associated with poor prognosis in acute myeloid leukemia. Oncology letters. 2018;15(5):6671–7.
14. Bartholomae S, Gruhn B, Debatin KM, Zimmermann M, Creutzig U, Reinhardt D, et al. Coexpression of multiple ABC-transporters is strongly associated with treatment response in childhood acute myeloid

leukemia. Pediatric blood & cancer. 2016;63(2):242–7.

15. Robey RW, Pluchino KM, Hall MD, Fojo AT, Bates SE, Gottesman MM. Revisiting the role of ABC transporters in multidrug-resistant cancer. Nature Reviews Cancer. 2018;18(7):452–64.
16. Damiani D, Tiribelli M, Raspadori D, Michelutti A, Gozzetti A, Calistri E, et al. The role of MDR-related proteins in the prognosis of adult acute myeloid leukaemia (AML) with normal karyotype. Hematological oncology. 2007;25(1):38–43.
17. Michieli M, Damiani D, Ermacora A, Masolini P, Raspadori D, Visani G, et al. P-glycoprotein, lung resistance-related protein and multidrug resistance associated protein in de novo acute non-lymphocytic leukaemias: biological and clinical implications. British journal of haematology. 1999;104(2):328–35.
18. Vakiti A, Mewawalla P. Acute Myeloid Leukemia. StatPearls [Internet]. 2020.
19. Li B, Tang H, Cheng Z, Zhang Y, Xiang H. The Current Situation and Future Trend of Leukemia Mortality by Sex and Area in China. Frontiers in Public Health. 2020;8:932.
20. Estey E, Kantarjian H, Keating M. Therapy for acute myeloid leukemia. Hematology: Basic Principles and Practice 4th ed Philadelphia, Pa: Elsevier. 2005:1099–120.
21. Rees J, Swirsky D, Gray R, Hayhoe F. Principal results of the Medical Research Council's 8th acute myeloid leukaemia trial. The Lancet. 1986;328(8518):1236–41.
22. Leith CP, Kopecky KJ, Chen I-M, Eijdems L, Slovak ML, McConnell TS, et al. Frequency and clinical significance of the expression of the multidrug resistance proteins MDR1/P-glycoprotein, MRP1, and LRP in acute myeloid leukemia. A Southwest Oncology Group Study. Blood, The Journal of the American Society of Hematology. 1999;94(3):1086–99.
23. Legrand O, Simonin G, Beauchamp-Nicoud A, Zittoun R, Marie J-P. Simultaneous activity of MRP1 and Pgp is correlated with in vitro resistance to daunorubicin and with in vivo resistance in adult acute myeloid leukemia. Blood, The Journal of the American Society of Hematology. 1999;94(3):1046–56.
24. van den Heuvel-Eibrink MM, van der Holt B, Burnett AK, Knauf WU, Fey MF, Verhoef GE, et al. CD34-related coexpression of MDR1 and BCRP indicates a clinically resistant phenotype in patients with acute myeloid leukemia (AML) of older age. Annals of hematology. 2007;86(5):329–37.
25. Ebeed SA, Sadek NA, Zaher ER, Mahmoud MM, Nabil G, Elbenhawy SA. Role of MRP-1 and GST-Pi in MDR and their inhibition by indomethacin in AML. Alexandria Journal of Medicine. 2017;53(3):251–9.
26. Filipits M, Stranzl T, Pohl G, Heinzl H, Jäger U, Geissler K, et al. Drug resistance factors in acute myeloid leukemia: a comparative analysis. Leukemia. 2000;14(1):68–76.
27. Altenberg GA. Structure of multidrug-resistance proteins of the ATP-binding cassette (ABC) superfamily. Current Medicinal Chemistry-Anti-Cancer Agents. 2004;4(1):53–62.
28. Salvia AM, Cuviello F, Coluzzi S, Nuccorini R, Attolico I, Pascale SP, et al. Expression of some ATP-binding cassette transporters in acute myeloid leukemia. Hematology reports. 2017;9(4).

29. Legrand O, Perrot JY, Simonin G, Baudard M, Cadiou M, Blanc C, et al. Adult biphenotypic acute leukaemia: an entity with poor prognosis which is related to unfavourable cytogenetics and P-glycoprotein over-expression. British journal of haematology. 1998;100(1):147–55.
30. Mahjoubi F, Golalipour M, Ghavamzadeh A, Alimoghaddam K. Expression of MRP1 gene in acute leukemia. Sao Paulo Medical Journal. 2008;126:172–9.
31. Kolesnikova M, Sen'kova A, Tairova S, Ovchinnikov V, Pospelova T, Zenkova M. Clinical and prognostic significance of cell sensitivity to chemotherapy detected in vitro on treatment response and survival of leukemia patients. Journal of personalized medicine. 2019;9(2):24.
32. Abel B, Murakami M, Tosh DK, Yu J, Lusvarghi S, Campbell RG, et al. Interaction of A3 adenosine receptor ligands with the human multidrug transporter ABCG2. European Journal of Medicinal Chemistry. 2022:114103.
33. Huang Y, Hu J, Lu T, Luo Y, Shi J, Wu W, et al. Acute myeloid leukemia patient with FLT3-ITD and NPM1 double mutation should undergo allogeneic hematopoietic stem cell transplantation in CR1 for better prognosis. Cancer management and research. 2019;11:4129.
34. Boddu PC, Kadia TM, Garcia-Manero G, Cortes J, Alfayez M, Borthakur G, et al. Validation of the 2017 European LeukemiaNet classification for acute myeloid leukemia with NPM1 and FLT3-internal tandem duplication genotypes. Cancer. 2019;125(7):1091–100.
35. Harada Y, Nagata Y, Kihara R, Ishikawa Y, Asou N, Ohtake S, et al. Prognostic analysis according to the 2017 ELN risk stratification by genetics in adult acute myeloid leukemia patients treated in the Japan Adult Leukemia Study Group (JALSG) AML201 study. Leukemia research. 2018;66:20–7.
36. Liu SB, Qiu QC, Bao XB, Ma X, Li HZ, Liu YJ, et al. Pattern and prognostic value of FLT 3-ITD mutations in Chinese de novo adult acute myeloid leukemia. Cancer science. 2018;109(12):3981–92.
37. Hirsch P, Tang R, Marzac C, Perrot J-Y, Fava F, Bernard C, et al. Prognostic impact of high ABC transporter activity in 111 adult acute myeloid leukemia patients with normal cytogenetics when compared to FLT3, NPM1, CEBPA and BAALC. Haematologica. 2012;97(2):241.
38. Sohrabi T, Ayatollahi H, Rokni M, Houshmand S, Zafari Z, Sadeghian MH, et al. Correlation of BCRP expression to NPM1 mutations in acute myeloid Leukemia. UHOD-Uluslararasi Hematoloji-Onkoloji Dergisi. 2018;28(3):180–6.
39. Kuss BJ, Eyre H, Lane S, Nancarrow J, Whitmore S, Callen D, et al. Deletion of gene for multidrug resistance in acute myeloid leukaemia with inversion in chromosome 16: prognostic implications. The Lancet. 1994;343(8912):1531–4.
40. Vasconcelos FC, de Souza PS, Hancio T, de Faria FCC, Maia RC. Update on drug transporter proteins in acute myeloid leukemia: Pathological implication and clinical setting. Critical reviews in oncology/hematology. 2021;160:103281.

Figures

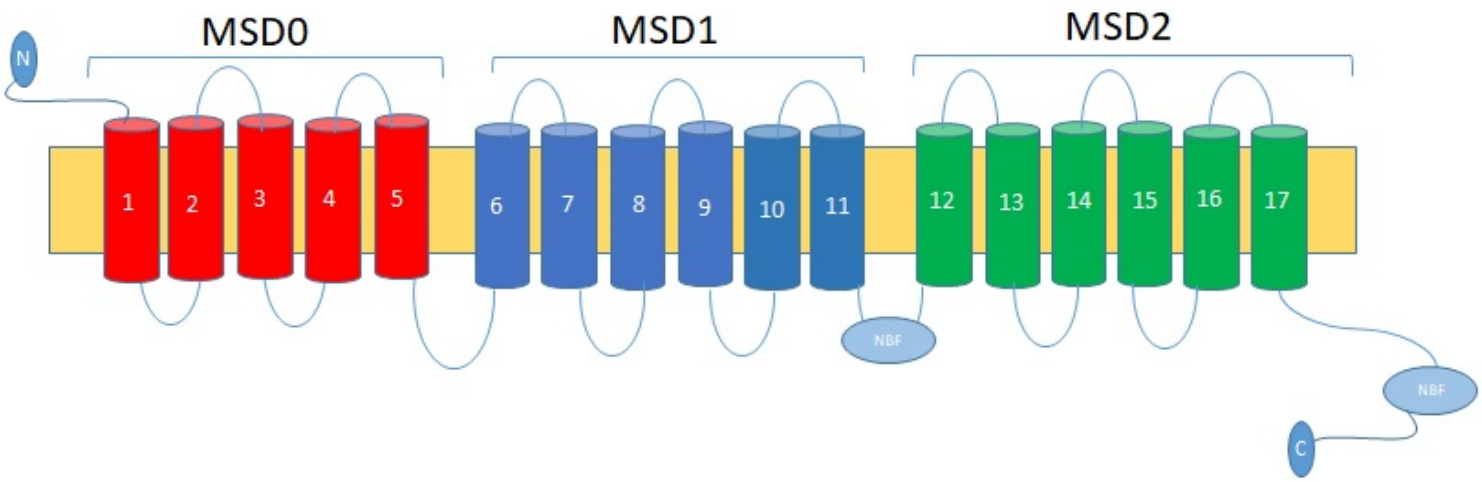

Figure 1

Structural representation of ABCC1. Membrane spanning domain consist of 11 helices. MSD 0 consist of 5 , MSD1 and MSD 2 consist 6 helices. NBF is attached to MSD 1 and MSD 2.

MSD: membrane spanning domain NBF: nucleotide binding fold

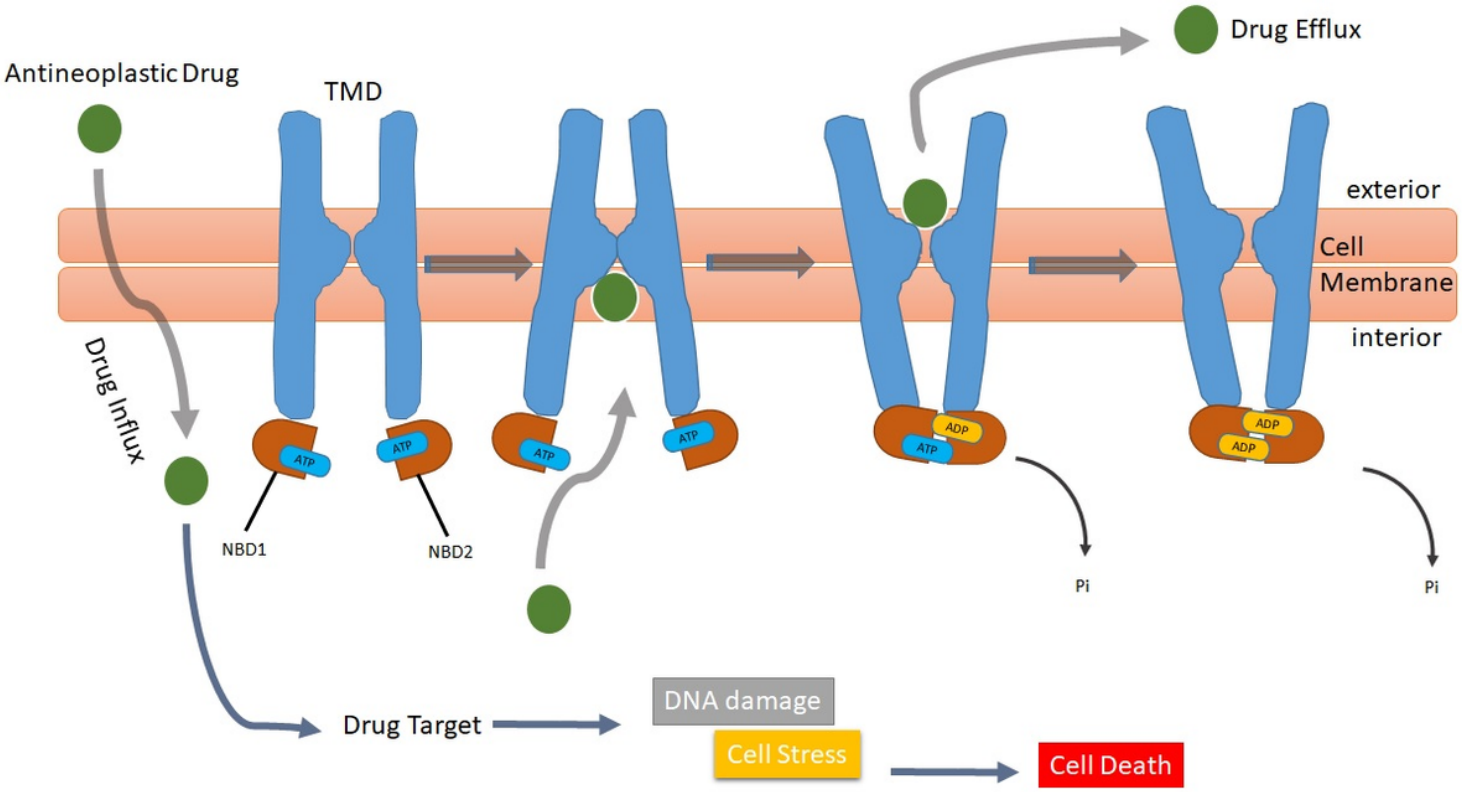

Figure 2

Mechanism of ABC transporters

TMD: Transmembrane domain, NBF: Nucleotide binding fold

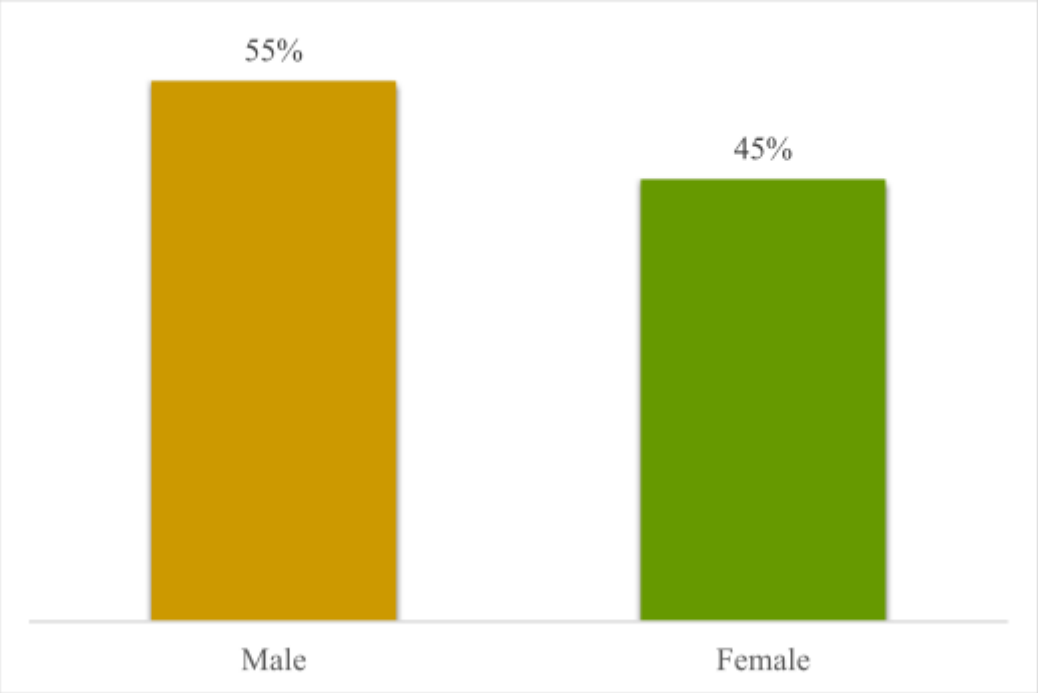

Figure 3

Gender wise distribution of study sample.

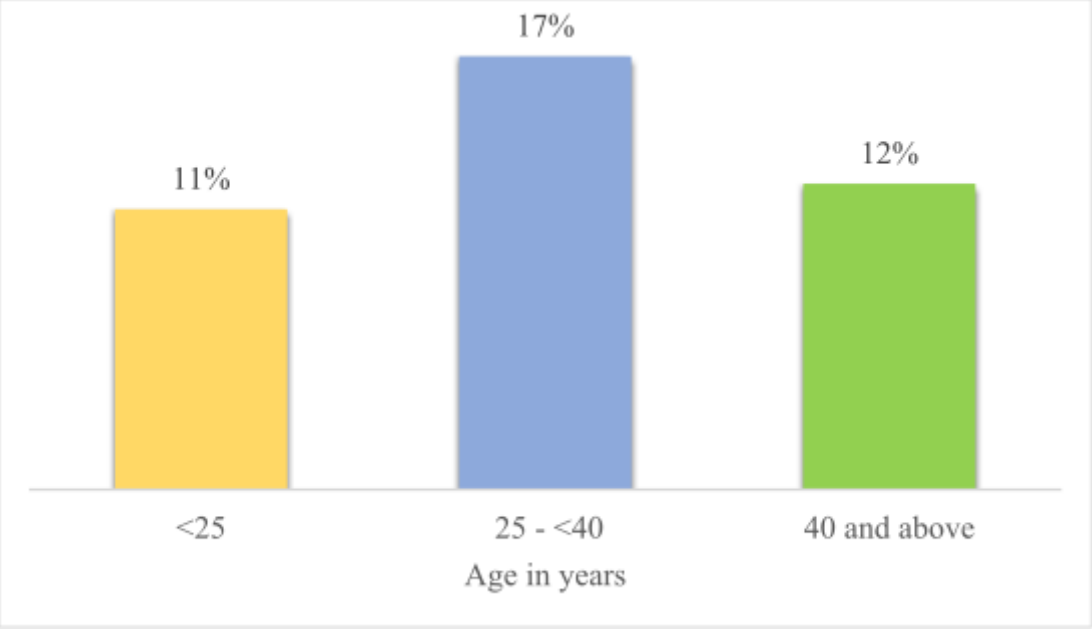

Figure 4

Age wise distribution of study sample.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Tables.docx