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Review

ATP-Binding Cassette transporters' gene expression in pediatric patients with acute leukemia; a comprehensive analysis of published reports through PubMed search engine

Narjes Mehrvar[1], Mohammad Esmaeil Akbari[1], Mohammad Reza Rezvany[2,3], Hasan Abolghasemi[4], Javad Saberynejad[5], Azim Mehrvar[5,6], Mohammad Faranoush[6,7], Ali Asghar Keramatinia[1,8], Reza Shekarriz-Foumani[8], Abolfazl Movafagh[1,9*]

[1] Cancer Research Center, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[2] Hematology department, Faculty of Allied Medicine, Iran University of Medical Sciences, Tehran, Iran
[3] Department of Oncology-Pathology, Immune and Gene Therapy Lab, Cancer Center Karolinska (CCK), Karolinska University Hospital Solna and Karolinska Institutet, Stockholm, Sweden
[4] Pediatric Congenital Hematologic Disorders Research Center, Research Institute for Childern`s Health, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[5] AJA University of Medical Sciences, Tehran, Iran
[6] MAHAK Hematology Oncology Research Center (MAHAK-HORC), MAHAK Hospital, Shahid Beheshti University of Medical Sciences, Tehran, Iran
[7] Pediatric Growth and Development Research Center, Institute of Endocrinology and Metabolism, Iran University of Medical Sciences, Tehran, Iran
[8] Department of Social Medicine, Medical School, Shahid Beheshti University of Medical Sciences and Health Services, Tehran, Iran
[9] Department of Medical Genetics, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

Correspondence to: movafagh_a@yahoo.com

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Abstract: Multidrug resistance based on ABC transporters' gene expression is one of the most important health challenges through chemotherapy of patients. This resistance can cause relapse or treatment failure. The goal of this conducted study was to evaluate the results of published reports which considered ABC transporters' gene expression in pediatric patients with acute leukemia. PubMed as a free search engine was chosen. The following Mesh terms were used as: "ATP-binding cassette transporters" OR "ABC-transporters*" AND "gene expression*" AND "leukemia" OR "ALL" OR "AML" OR "acute leukemia*". Age was set as an additional filter with the age range of birth to 18 years old. Initial screening was performed according to inclusion and exclusion criteria and the quality of the selected papers was assessed. Papers categorized into three sections as: pediatric patients with ALL (6 papers from 1998-2015); pediatric patients with AML (3 papers from 1992-2011) and pediatric patients with ALL and AML (7 papers from 1992-2014). Totally 1118 patients enrolled in the searched studies (ALL and AML: 488; ALL: 405; AML: 225). The common method for evaluating gene expression of ABC transporters was RT-PCR. More than 50% of the papers showed the influence of ABC transporters' gene expression on prognosis and treatment failures of patients. Despite controversial results, the gathered information in the current report serves as a comprehensive referential resource, which can be beneficial for future planning around this title, especially in developing countries.

Key words: ABC transporters, Acute leukemia, Gene expression, Prognosis.

Introduction

Primary resistance to anticancer agents is common in tumor cells (1). This event has been introduced as multidrug resistance (MDR) in patients with malignancy since 1970 (2). ATP-Binding Cassette (ABC) transporters are membrane-bound transport proteins which after recruiting ATP, can transport anticancer substrates into or out of tumor cells during chemotherapy (3). Some members of 49 ABC transporter genes, which are divided in 7 subfamilies, are responsible for MDR in cancer cells (4). ABC transporters play an important role through the mediation of MDR in patients with malignancy (4).

The major challenge through the treatment of patients with acute leukemia is chemo resistance (5). This resistance can lead to treatment's failure and poor outcome. In vitro studies showed high levels of mRNA expression of ABC transporters at the time of diagnosis in patients with leukemia (6, 7, and 8). By transporting cytostatic drugs into- or out of the cells, ABC transporters can cause MDR in patients with leukemia (5). Results of different studies considering this issue lead to a hypothesis that MDR in patients with acute leukemia can be due to the high expression of ABC transporter gene.

This review project designed to focus retrospectively on the results of papers which evaluated the gene expression of ABC transporters in patients with acute leukemia. As PubMed is a free search engine with accessibility to MEDLINE databases even in countries with sanction (9), we conducted this comprehensive study to

evaluate published reports with considered item. The results of this study can be access as a baseline data for researchers who are interested in planning future projects about the role of ABC transporters in patients with acute leukemia.

Methods

Electronic searches of published articles from 1970 to 2017 were done through PubMed search engine. The medical subject key terms which had been used were as follow:

"ATP-binding cassette transporters" OR "ABC-transporters*" AND "gene expression*" AND "leukemia" OR "ALL" OR "AML" OR "acute leukemia*". Asterisks on search terms allowed the specified search terms which were as the major topics of the article and could be in the title or statement of the purpose. The search items were filtered for the age range of birth to 18 years old.

A screen of the initial search according to mentioned terms and filters resulted on 46 articles. The primary evaluation of these articles was done based on their title and abstract and according to the following exclusion criteria: (I) studies which considered only adult patients; (II) studies pointing molecular techniques other than gene expression; (III) studies describing patients with leukemia and non-leukemia malignancies; (IV) letters to editor; (V) studies lacking specific age range and finally (VI) studies lacking any relevant data. After this first evaluation, 31 articles were selected, 4 of which were available as abstracts. Full text of other 27 articles was acquired and considered for further evaluations. Figure 1 shows the flowchart of qualification and review process which accessed to 16 full text papers for final evaluation.

After applying the exclusion criteria, the evaluation was done according to specified items such as the location where the study was conducted, duration of the study, the number of patients (based on new cases, individuals with complete remission and patients with relapse), control group, type of the ABC transporter studied, the technique which was used for gene expression evaluation, the type of sample (peripheral blood or bone marrow), the objective of the study and the general concept of the study.

Results

Pediatric patients with Acute Lymphoblastic Leukemia (ALL)

Totally 6 papers during 1998 to 2015 were published in PubMed about gene expression of ABC transporters in pediatric patients with ALL (10-15). Only 2 papers were from European countries and others were from Asia. The duration of study varied between published papers from 1 year to 13 years.

Altogether, 405 patients were considered in these papers: 335 new cases, 37 relapses and 33 complete remissions. Only 3 studies included a normal control group (healthy individuals).

Expression of *ABCC1* (12), *ABCB1* with *ABCC1* (10, 11, 14, 15) and *ABC1-6* (13) was evaluated. The method of evaluation was Real Time PCR in 5 studies (10-13, 15) except for 1 study (14) which evaluated the gene expression of *ABCC1* and *ABCB1* detected with monoclonal antibodies.

One study considered if there is any expression of *ABCC1* in enrolled patients (12), the other studies evaluated the correlation between gene expression and defined variants such as treatment/disease outcome, prognosis, pathological features, etc (10, 11, 13-15). Three studies showed a correlation of ABC transporters' gene expression and the evaluated variants (10, 13, 14) and the other 3 studies didn't conclude any relation (11, 12, 15) (Table I).

Pediatric patients with Acute Myeloid Leukemia (AML)

Three papers from USA and Germany were published in PubMed during 1992 to 2011 (16-18). In total, 225 pediatric patients were evaluated in these studies and most of them were new cases (97.8%). The expression of *ABCG2* (18), *ABCB1* (16, 17) and *ABCC1* (17) were evaluated in these projects. Gene expression was the main goal of the projects. One paper discussed the best technique for detecting gene expression in pediatric patients with AML. The characteristics of these papers are summarized in Table II.

Pediatric patients with ALL and AML

Seven published manuscript during 1992 to 2014 were the result of search in PubMed engine (19-25) according to inclusion and exclusion criteria of the project. Totally 488 patients with ALL and AML (ALL: 62.1%; AML: 37.9%) were enrolled in these projects. Only 2 types of patients as new cases (ALL: n=210; AML: n=155) and relapse individuals (ALL: n=93; AML: n=30) were considered. Two papers from Belarus also comprised their results with normal people as control group (19, 23). The expression of *ABCC1, ABCB1, ABCB5* and *ABCG2* was evaluated by RT-PCR in 6 of the papers (20-25) and the expression was assessed with monoclonal antibody methods in one of the papers (19). The main purpose of these manuscripts was to determine the correlation between ABC transporters' gene expression and prognosis of the patients. Most of the conclusions showed a direct correlation between high levels of *ABC transporters* expression and poor prognosis (19-21, 23-24). The main characteristics of

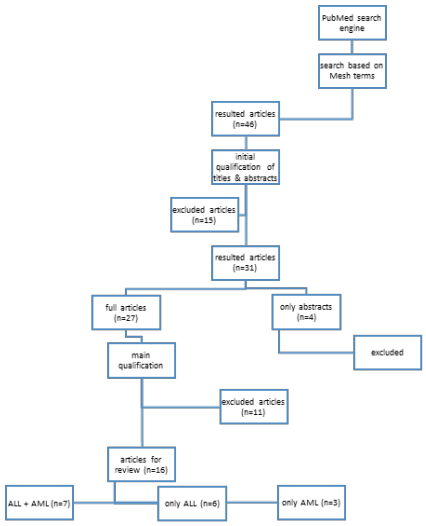

Figure 1. flowchart of articles' qualifications and review.

Table 1. evaluation of ABC transporters' gene expression in pediatric patients with ALL.

Place of study	Duration of study	Individuals			Control group	ABC transporters			Methods		Samples		Objective	Conclusion
		New case	CR	Relapse		C1	B1	C1-6	RT-PCR	Mab	PB	BM		
India[10]	4 yrs.	125	33	9	12 (NHL & normal)	+	+	-	+	-	+	+	Correlation of gene expression and pathological features	Gene expression was higher in patients with relapse, new cases and CR respectively
India[11]	NA	32	-	-	-	+	+	-	+	-	+	+	Correlation of gene expression and treatment's outcome	No correlation between gene expression and treatment outcome
Germany[12]	NA	58	-	28	NI (normal)	+	-	-	+	-	+	+	Gene expression in pediatric ALL	No differences through gene expression between relapsed patients and new cases. No prognostic importance of ABC transporters
Netherland[13]	13 yrs.	56	-	-	-	-	-	+	+	-	+	+	Correlation of gene expression and prognosis	High gene expression of *C1, C3* and *C5* that related with unfavorable outcomes
Malaysia[14]	NA	19	-	-	-	+	+	-	-	Anti-gene Ab	+	+	Correlation of gene expression and functional activity	The mentioned method is good for evaluating the gene expression
India[15]	1 yr.	45	-	-	7 (normal)	+	+	-	+	-	+	-	Correlation of gene expression at diagnosis and early response	No relation between gene expression and early response

NA: Not Indicated; CR: Complete Remission; NHL: Non Hodgkin Lymphoma; RT-PCR: Real Time Polymerase Chain Reaction; Mab: Monoclonal Antibody; PB: Peripheral Blood; BM: Bone Marrow

Table 2. evaluation of ABC transporters' gene expression in pediatric patients with AML.

Place of study	Duration of study	Individuals			Control group	ABC transporters			Methods		Samples		Objective	Conclusion
		New case	CR	Relapse		*C1*	*B1*	*G2*	RT-PCR	Mab	PB	BM		
USA[16]	NA	11	2	3	2 (MDS)	-	+	-	-	JSB1, HYB241, C219, MRK16	+	+	Evaluation of gene expression by four techniques	There were High incidence of false positive reactions by these four techniques
Germany[17]	6 yrs.	124	-	-	-	+	+	-	-	MRK 16 Ab	-	+	Correlation of gene expression and prognosis	No single gene expression related with OS but combination of genes expression reduce OS
USA[18]	3 yrs.	85	-	-	-	-	-	+	+	-	-	+	Correlation of gene expression and prognosis	No relation between gene expression and prognosis

NA: Not Applicable; CR: Complete Remission; MDS: Myelodysplastic Syndrome; RT-PCR: Real Time Polymerase Chain Reaction; Mab: Monoclonal Antibody; PB: Peripheral Blood; BM: Bone Marrow; OS: Overall Survival

Table 3. evaluation of ABC transporters' gene expression in pediatric patients with ALL & AML.

Place of study	DOS	Individuals				Control Group	ABC transporters				Methods			Samples		objective	conclusion
		New cases		Relapse													
		ALL	AML	ALL	AML		*C1*	*B1*	*B5*	G2	RT-PCR	Mab	NB	PB	BM		
Belarus[19]	NA	70	36	19	-	30 normal	-	+	-	-	-	FITC-labeled 17F9	-	-	+	Correlation of gene expression and prognosis	Expression: higher in AML than ALL; higher in relapse ALL than new cases
Germany[20]	NA	6	4	25	4	-	-	+	-	-	+	-	+	+	+	Correlation of gene expression and multidrug resistance	Significant relation between high expression and poor prognosis
USA[21]	2 yrs.	-	-	14	15	-	-	+	-	-	+	-	-	+	+	Correlation of gene expression and multidrug resistance	High gene expression in relapsed patients
Korea[22]	1 yr.	32	39	-	-	-	+	+	-	-	+	-	-	-	+	Correlation of gene expression and outcome	No relation between gene expression and outcome
Belarus[23]	NA	85	65	35	11	CLL (27 NC; 51 treated)	-	+	-	+	+	-	-	-	+	correlation of gene expression and outcome	Significant relation between gene expression and low complete remission, overall survival and outcome
Brazil[24]	NA	13	4	-	-	-	+	+	-	-	+	-	-	+	+	Correlation of gene expression and prognosis	Significant relation between gene expression and drug resistance
Egypt[25]	NA	4	7	-	-	-	-	+	+	-	+	-	-	+	+	Correlation of gene expression and prognosis	Variable patterns in relations of gene expression and prognosis

DOS: Duration Of Study; NA: Not Applicable; RT-PCR: Real Time Polymerase Chain Reaction; Mab: Monoclonal Antibody; NB: Norton Blot; PB: Peripheral Blood; BM: Bone Marrow;

considered papers are delineated in table III.

Discussion

The superfamily of transporter proteins, ABC binding cassette proteins, specially *ABCB1* and *ABCC1* are involved in extracellular efflux of chemotherapy drugs mechanisms (26). One of the most important causes of treatment failures in patients with acute leukemia are the mechanisms involved in multidrug resistance (27). Chemotherapy resistance can lead to poor outcome and prognosis in spite of recent advances in patients' treatment (28). Literature and reviews revealed different and controversial conclusions through the relation between expression of ABC transporters' gene and prognosis or outcome in patients with acute leukemia.

Treatment of pediatric patients with acute leukemia is one of the major challenges in health and management system of developing countries. Multidrug resistance phenomenon based on ABC transporters gene expression is the most common factor leading to treatment failures or poor prognosis, outcome and survival of patients. Due to controversial results from different studies, many issues remain to address in this field.

In a country such as Iran, the first step for designing an experimental project regarding expression of *ABC transporters* in pediatric patients with acute leukemia, is to perform an accurate and comprehensive literature review. One of the barriers through scientific search is accessibility to full articles of searched papers from different search engines. The only free search engine is PubMed. According to mentioned information this original study designed to evaluate the concept, results, data and final conclusion of reports which were available via PubMed search engine to-date, without implementing a time filter.

In 1999, Dhooge and colleagues by immunohistochemistry method evaluated the expression of *ABCB1* protein in pediatric new cases and relapses patients with ALL. They concluded that overexpression of *ABCB1* could cause poor prognosis especially in individuals with newly diagnosed disease (29). One year later in 2000, Wuchter et al, considered the expression of *ABCB1* on patients with acute leukemia. Their results were in contradiction with Dhooge et al. they revealed that there is not any relation between gene expression of *ABCB1* and prognosis in patients with acute leukemia (30).

Fujimaki and colleagues designed a project to evaluate the gene expression of *ABCB1* and *ABCC1* in patients with ALL and AML. The methods of the evaluation were flow cytometry and RT-PCR. The analyses of the results revealed that *ABCB1* was expressed higher in patients with AML and mainly in patients with relapsed disease. Also, they noted that there was not any significant relation between clinical outcomes and expression of *ABCC1* in patients with acute leukemia (31). Two years later Schaich et al considered the expression of *ABCB1* and *ABCC1* in patients with AML who were as new cases or secondary AML. Their results supported that expression of these two genes influenced complete remission after treatment in patients (32).

In 2005, two different studied with flow cytometry method had been done by Benderra et al (33) on 85 patients with de novo AML and Olson et al (34) on 295 new cases with ALL. The results of those two studies were not the same. As Benderra et al concluded that expression of *ABCB1* could lead to treatment failure, but Olson et al showed that there is no significant relation between the expression of *ABCB1*, *ABCC1* and treatment failure in the considered patients.

Other studies which did not conclude any significant relation between the influence of gene expression of ABC transporters and patients' outcome, prognosis or treatment failures were done by Fedasenka et al (35) and Grotel et al (36) on patients with ALL at 2008, and also by Scheiner et al through patients with AML at 2012 (37).

Literature review acknowledged that there were several studies which approved the influence of ABC transporters' gene expression on outcome, prognosis or treatment failure of patients with acute leukemia. (38-42). Among these studies, Huh et al, Stycsynski et al and Cahuhan et al recruited patients with ALL and AML in their projects; De Figueiredo Pontes et al only evaluated patients who had AML; finally El-Sharnouby considered patients with ALL. Methods of their evaluation for gene or protein expression were Nested-PCR, RT-PCR and flow cytometry.

Through a comprehensive literature review, we show that reports about evaluating gene expression of ABC transporters through pediatric patients with ALL and AML were more than pediatric patients with ALL and then after with AML. Recent reports indicated that gene expression in patients with relapse was higher than in new cases or patients who completed their therapy without any failure.

Because of controversial reports, there should be future planning to evaluate the relation of gene expression and treatment's outcomes in patients with acute leukemia. Also the important issue was that nearly more than 50% of reported papers were from regions other than developing countries. So this title still needs more evaluation in these parts. Another suggestion of the authors is considering the relation of ABC transporters' gene expression on patients with AML more than previous studies.

Finally, the results of this project serve as a comprehensive referential resource, which can be beneficial for future's planning considering the influence of ABC transporters' gene expression on the treatment and management of pediatric patients with acute leukemia in developing countries.

Conflict of interest

Authors approve that there is not any conflict of interest.

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