International Journal of Hematology and Therapy

OMMEGA Publishers
Answering Intelligence

ISSN:2381-1404
OPEN ACCESS

Research Article

Characterization of Mir-92b, 1275 and 551 in Patients with Acute Myeloid Leukemia and Their Association with Acute Graft Versus Host Disease after Hematopoietic Stem Cell Transplantation

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Abstract

Background: MicroRNAs (MiRs) play a dual role in Acute Myeloid Leukemia (AML); hence, we can except both down and up-regulation of MiRs in latter patients. We analyzed the expression of MiR1275, MiR-551 and MiR-92b in 100 newly diagnosed AML patients before and after chemotherapy with the aim to determine their role in diagnosis and prognosis of AML patients.

Materials and Methods: MiR-1275, MiR-551, and MiR-92b MiRs expression level of 100 newly diagnosed AML patients were analyzed prior and following chemotherapy via SYBR Green Real-Time PCR.

Results: Expression of MiR-92b and MiR-551 significantly increased (7.4-fold, 10.5-fold respectively) in AML patients following chemotherapy compared to baseline value at the time of diagnosis prior to chemotherapy (P=0.02, P=0.004, respectively). Conversely, MiR-1275 expression decreased significantly following chemotherapy (P=0.001). Also, the results showed that the mean expression level of MiR-92b and MiR-551 were significantly increased in the high-risk group compared to intermediate one (P=0.001, P=0.001, respectively).

Conclusion: Taken together, Mir-1275, Mir-551, Mir-92b expression in AML patients is associated with cytogenetics, molecular alterations, marrow morphology, and clinical outcomes the correlation of studied MiRs with aGvHD was insignificant.

Key words: Acute Myeloid Leukemia ; microRNA; MiR-1275; MiR-551; MiR-92b; Acute Graft versus Host Disease (aGvHD)

Introduction

MicroRNAs (MiRs) are small non-coding RNAs containing 19-25 nucleotides, which are being utilized in prognosis and diagnosis of many diseases[1-3]. These specific RNAs are the main gene expression regulators that normalize cellular proliferation, differentiation, and apoptosis. And they have been meticulously investigated in the past two decades[4,5]. Although it is expected to detect MiRs in cells, these RNAs had been spotted in cancer patients' serum. For most parts, the detected MiRs were related to the chromosome regions, associated with cancers[4]. MiRs play dual role in cancer, some play as tumor suppresser like MiRs 15a/16-1 cluster in lung cancer, some function as oncogenes such as MiR 17-92 cluster and MiR-155/BIC in lymphoma. Therefor we can except both down and up regu-

Received date: January 24, 2020
Accepted date: February 04, 2020
Published date: February 07, 2020

Citation: Mani, R., et al. Characterization of Mir-92b,1275 and 551 in Patients with Acute Myeloid Leukemia and Their Association with Acute Graft Versus Host Disease after Hematopoietic Stem Cell Transplantation. (2020) Int J Hemat Ther 6(1): 1-6.

lation of MiRs amongst cancer patients[6-13]. MiRs have shown a dual role in cancer, some play as tumor suppresser like MiRs 15a/16-1 cluster in lung cancer, others function as oncogenes, such as MiR 17-92 cluster and MiR-155/BIC in lymphoma[14]. Therefore, we can except both down and up-regulation of MiRs amongst cancer patients. Regarding the function of MiRs, these RNAs have been used not only to diagnose cancers, but also in determining the prognosis[15].

Therefore mentioned role was used for the first time in a study by Lawrie et al. in patients with lymphoma, which revealed the association of survival rate with MiR-21[5].

Another defined role for MiRs was to classify cancers since this method turned out to be more accurate than previous ones such as mRNA profiling. In this regard, classification of poorly differentiated AML was enhanced by reviewing the expressed MiRs[16]. AML as the most common type of leukemia[17] has four major chromosome translocation of which t(8;21), t(15;17), and inv(16) appear to have a better outcome than MLL/11q23 translocation[18]. Although eAML prognosis is based on the mentioned translocations, result inconsistencies calls for a more valid method such as the evaluation of MiRs. MiRs signature is detected in AML subtypes by identifying significant and unique MiR expression for each type[16]. For instance up-regulation of MiR-12, MiR-134, MiR-299–5p, MiR-323, MiR-376a and MiR-382 were shown in serum of AML patients who had t(15;17) chromosome translocation[16,18]. With more than 2000 MiRs identified, many more are still expected to be discovered and used not only as an indicator of prognosis and diagnosis, but also as indictors of response to treatment. And hopefully, by targeting MiRs we will be able to reach cancer therapy in the near future[17,19,20]. To provide a plenary insight into MiR1275, MiR-551 and MiR-92b among AML patients regarding diagnosis, prognosis, response to treatments and transplant and survival. Therefore, we analyzed the expression of 3 lesser knowns and studied MiRs in AML patients before and after chemotherapy.

Materials and Methods

Patients

In this cross-sectional study, 100 newly diagnosed AML adult patients were recruited from Namazi Hospital, affiliated to Shiraz University of Medical Sciences from February 2014 to March 2017. The AML diagnosis was confirmed by oncologists using morphology, cytochemistry, and immunophenotyping. Those with any previous history of malignancy and chemotherapy, chronic diseases and transplant were excluded; hence, 2 patients left the study. All patients received standard induction chemotherapy, which consisted of daunorubicin and cytarabine, also, For M3 patients, arsenic trioxide and ATRA in 2 divided doses in addition to standard induction chemotherapy regiment according to the manufacturer's instructions. as previously described Briefly[21-24].

Forty-two patients received Hematopoietic stem cell transplantation (HSCT) from the related HLA-matched donors. Sub-group to acute graft versus host disease (aGvHD) experienced and not-experienced (non-aGvHD) HSCT patients. Acute graft versus host disease (aGvHD) was classified according to the classic Glucksberg–Seattle criteria and the International Bone Marrow Transplant Registry[25]. Eighteen patients developed aGvHD, eleven patients had a low grade (grade I+II) aGvHD, and seven cases developed high grade (grade III+IV) of aGvHD. All procedures were in accordance with the Helsinki protocol of 1975 and approved by the Ethical Committee of Shiraz University of Medical Sciences (Shiraz, Iran) (Ethics committee code #94-01-104-11279).

Cytogenetic Analysis

Cytogenetic analysis was performed according to the National Comprehensive Cancer Network (NCCN) guidelines[26]. Chromosomal abnormalities were tested by reverse transcriptase polymerase chain reaction (RT-PCR) for AML1-ETO and CB-FB-MYH11. Patients who were negative for these chromosomal abnormalities were considered as CN-AML.

Sample collection and Ribonucleic acid isolation

Five-milliliter peripheral blood was collected in Ethylenediaminetetraacetic acid (EDTA)-containing tubes from each patient at the time of diagnosis prior to chemotherapy treatment and also healthy individuals. The peripheral blood mononuclear cells (PBMCs) were isolated from each patient and controls using Ficoll-hypaque density gradient centrifugation. Total RNA was extracted by TRIZOL reagent (Invitrogen) according to the manufacturer's instructions as previously described briefly[21-23].

SYBR green real-time Polymerase chain reaction

For the quantitative analysis of MiR-1275, MiR-551, and MiR-92b MiRs expression level, the SYBR Green Real-Time PCR method was performed using SYBR Premix Ex TaqTM II (Tli RNaseH Plus) (Takara, Japan) and designed primers specific for each MiRNA in an iQ5 thermocycler (BioRad Laboratories, USA) according to the manufacturer's instructions. As previously described Briefly[21-23].

Table 1: The Primers and PCR condition for the MiR-1275-, MiR-551, MiR-92band GAPDH gene

Gene	Primer sequences (5'->3')	Thermocycling condition
MiR-1275 :F	TGTTTGGGTGGGGGAGAG	94 ◦ C/2 min, 40 cycles of 94°C/30 sec, 56.5°C/20 sec and 70°C/30 sec
MiR-1275 :R	GTGCAGGGTCCGAGGT	
MiR-92b :F	GGTTTAGGGACGGGACG	94 ◦ C/2 min, 40 cycles of 95°C/30 sec, 57.5°C/20 sec and 70°C/30 sec
MiR-92b :R	GTGCAGGGTCCGAGGT	
MiR-551:F	GGGGAAATCAAGCGTGGG	94 ◦ C/2 min, 40 cycles of 94°C/10 sec, 56.5°C/20 sec and 72°C/15 sec
MiR-551:R	GTGCAGGGTCCGAGGT	
GAPDH:F	GGACTCATGACCACAGTCCA	95 ◦ C/2 min, 40 cycles of 95°C/30 sec, 57.5°C/20 sec
GAPDH:R	CCAGTAGAGGCAGGGATGAT	

Statistical Analysis

Data were analyzed by SPSS software, version 18. The differences in the mean expression level of MiR-1275-, MiR-551 and MiR-92b before and after chemotherapy were compared via paired t-test. Mean expression level of MiR-1275, MiR-551, and MiR-92b dicer regarding laboratory data were analyzed

by Chi-square test. The mean expression level of MiR-1275, MiR-551 and MiR-92b were compared between patients based on response to chemotherapy treatment, cytogenetic aberration and FAB subtypes by independent t-test. P-values less than 0.05 were considered to be statistically significant.

Results

A hundred newly diagnosed AML patients with a mean age of 38±2.4 years (20-86) were studied of whom 52.5% were female. Details of demographic and laboratory characteristics of patients are shown in Table 2.

Table 2: Demographic and laboratory information of AML patients

Gender n(%)	
Male	48 (48.0)
Female	52 (52.0)
FAB classification n(%)	
M0	13 (13.0)
M2	40 (40.0)
M3	22 (22.0)
M4	11 (11.0)
M5	12 (12.0)
M6	2 (2.0)
M7	0 (0)
Median age years	45.4 (19-85)
Blood count	
White blood cell (×10^6)	38.6(0.9-300)
Hemoglobin (g/dl)	8.1 (3.8-14.7)
Platelet (× 10^6)	51 (3-380)
Response rate after treatment n(%)	
Patients with chemotherapy response	53 (53.0)
Patients without chemotherapy response	47 (47.0)
Cytogenetic/molecular risk n(%)	
Favorable risk	22 (22.0)
Intermediate risk	45 (45.0)
Poor risk	33 (33.0)

Changes in MiR-1275, MiR-551 and MiR-92b expression amongst AML patients following chemotherapy

The mRNA expression of MiR-1275, MiR-551 and MiR-92b were measured before and after chemotherapy. After the statistical analysis, our results revealed that the expression of MiR-92b and MiR-551 significantly increased (7.4 fold, 10.5-fold respectively) in AML patients following chemotherapy compared to baseline value at the time of diagnosis prior to chemotherapy (1.02±0.98 vs. 3.9±0.79; P=0.02, 95% confidence interval (CI): -5.1 to -0.41 for MiR-92b), (1.2±0.80 vs. 4.6±0.82; P=0.004, 95% CI: -5.6 to -1.09 for MiR-551). Conversely, MiR-1275 expression decreased significantly following chemotherapy (2.9±0.82vs. 1.4±0.84; P=0.001, 95% CI: -0.76 to -3.8).

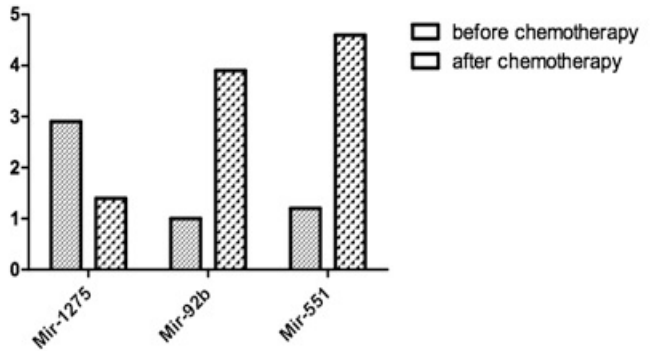

Figure 1: Change in MiR-1275, Mir-92b and MiR-551 expression following chemotherapy in AML patients

MiR-1275, MiR-551 and MiR-92b expression in HSCT patients and development of the aGvHD

The mean expression of MiR1275, MiR-551 and MiR-92b were compared between patients with and without aGvHD. Our results demonstrated that MiR-1275, MiR-551 and MiR-92b gene expression levels were increased in patients who developed aGvHD in comparison with those without aGvHD, albeit the difference was not statistically significant (0.14±3.7vs. 3.4±1.2; P=0.3, 95% CI: -10.4 to 3.8 for MiR -1275), (-1.03±4.3 vs. 3.5±1.3; P=0.2, 95% CI: -12.8 to 3.6 for MiR-92b) (-0.2±3.7vs. 2.9±0.9; P=0.3, 95% CI: -10 to 3.6 for MiR-551). In addition, MiR1275, MiR-551 and MiR-92b were overexpressed in HSCT (hematopoietic stem cell transplantation) patients with high grade aGvHD (grade III-IV) compared to those patients who developed low grade (grade 0-II) aGvHD, although the difference was not statistically significant (-2.3±8.1vs. 2.1±2.2; P=0.5, 95% CI: -11.7 to 20.7 for MiR-1275), (-3.8±9.6 vs. 1.2±2.3; P=0.5, 95% CI: -13.2 to 24.2 for MiR-92b) (-2.4±7.9vs. 1.4±2.6; P=0.6, 95% CI: -12.2 to 20.1 for MiR-551)

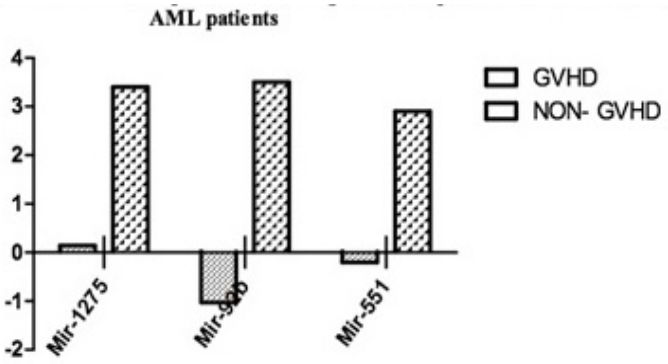

Figure 2: Change in MiR-1275, Mir-92b and MiR-551 expression following between patients with and without aGvHD in AML patients

MiR1275, MiR-551, and MiR-92b in AML patients and response to treatment

The baseline expression level of MiR-1275, MiR-551 and MiR-92b were evaluated in AML patients according to their response to treatment. Our results demonstrated that MiR-1275, MiR-551 and MiR-92b gene expression levels were increased in AML patients who did not respond to chemotherapy in comparison with those who responded to chemotherapy, albeit the difference was not statistically significant (2.5±1.4vs. 3.4±0.79; P=0.5, 95% CI: -4.1 to 2.3 for MiR-1275),(-0.59±1.5 vs. 1.4±1.1; P=0.6, 95%

CI: -4.7 to 3.06 for MiR-92b), (0.33±1.3 vs. 2.2±0.75; P=0.2, 95% CI: -5.1 to 1.2 for MiR-551).

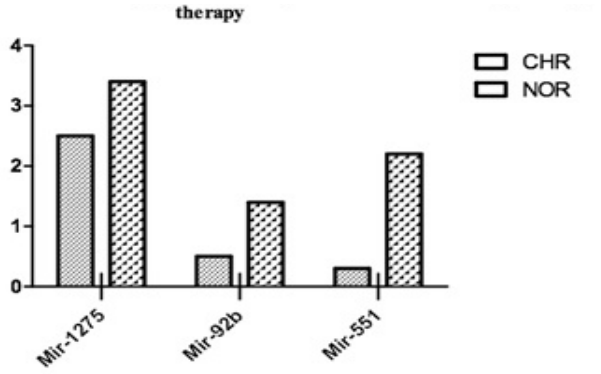

Figure 3: miR-1275, miR-92b, miR-551 expression level in AML patients and response to chemotherapy; CHR: AML patients who responded to primary induction therapy, NOR: AML patients who did not respond to primary induction therapy

MiR1275, MiR-551 and MiR-92b expression according to cytogenetic status and FAB groups

The expression level of MiR1275, MiR-551 and MiR-92b were compared within AML patients based on their cytogenetic abnormalities. Among all AML patients, 33 (30.5%) had a FLT3-ITD mutation. Based on the generally genetic risk stratification, AML patients were divided into three groups; favorable, intermediate and high-risk. Accordingly, 33 patients were included in high risk, 45 in intermediate and the remaining 22 in favorable risk groups. The results showed that the mean expression level of MiR-92b and MiR-551 were significantly increased in high-risk group compared to intermediate one (-0.85±1.1 vs. 5.5±0.67; 95%CI: -9.03 to -3.8, P=0.001), (-2.2± 0.81vs. 4.1±0.65; 95%CI: -8.3 to -4.2, P=0.001). The mean expression level of MiR-1275 did not significantly change between high-risk group compared to intermediate one, (P>0.05). Mean expression level of MiR-1275, MiR-551 and MiR-92b were compared within risk stratification group since the FAB group of some AML patients was not defined, we divided AML patients into M3 and non-M3 groups and compared the expression of MiR-1275, MiR-551 and MiR-92b amongst them. Our results demonstrated that the expression level of MiR-1275, MiR-551 and MiR-92b did not differ between AML patients with M3 and non-M3 FAB subtypes (P>0.05).

Discussion

MiRs and its role in cancer was first discovered in hematological malignancies, and later on many studies revealed the potential role of these RNAs in diagnosis, demonstrating prognosis, response to therapy, and classification of many malignancies[4,20]. In the current study, we assessed the expression of the three lesser-known MiRs (MiR-1275, MiR-551 and MiR-92) amongst AML patients by considering the mean differences of MiRs expression before and after chemotherapy. These MiRs were also evaluated in AML patients with or without aGVHD, AML M3 and none-M3 and cytogenetic abnormalities. In our study, MiR-551 and MiR-92 increased significantly after chemotherapy, an adverse result was detected in MiR-1275. Non-significant increase of all three MiRs were observed in those with aGVHD. As for classification, there was a significant correlation between two of the studied MiRs expression amongst high-risk patients in comparison with intermediate risk. Also, specific MiR pattern was seen in some of the mutations. Previous studies showed that not only MiRs can differentiate leukemia subtypes, but they can also determine cytogenetic subtypes of AML[14]. Identified cytogenetic subtypes of AML are the core factors in predicting the outcomes by establishing treatment methods[27,28]. With respect to the known role of MiRs in numerous aspects of AML many have been studied to find possible coloration between its expression and diagnosis[25,29]. AML classification by MiRs was proven by Jongen et al. He also detected specific MiRs in subgroups of AML with different cytogenic characteristics[19]. Following his leads, we measured MiR-1275 expression between high-risk groups, intermediate and favorable, which showed no correlation exists. So far, MiR-1275 has not been studied in AML. This RNA seems to be an indicator of high grade Oral squamous cell carcinoma with nodal invasion[30]. MiR-1275 were even named as tumor suppressor and appeared to control hepatocellular carcinoma tumor by Fawzy et al[31].

When we studied this RNA amongst our AML patients the expression level was considered high, which decreased significantly after chemotherapy, and increased insignificantly amongst those who did not respond to chemotherapy. The aforementioned result suggests the possible role for this MiR as an indicator for response to treatment. MiR-1275 was not different between M3 and non-M3 patients, but was significantly higher amongst those with MLLT3-MLL mutation and chromosome abnormality of (8:21) (15:17) (inv 16), which justifies its role in diagnosis and classification of AML patients. MiRs were also considered in leukemic patients with HSCT, amongst those we can mention monitoring MiR-155 in patients who developed GVHD by Chen et al. They showed that the mentioned MiR was associated with high rates of GVHD[32]. Also, we detected MiR-1275, which was insignificantly higher amongst those with high-grade aGVHD. De Leeuw et al. evaluated another MiR in AML patients: MiR-551b. He showed a correlation between high expression of this MiR and poor prognosis in AML patients, and hypothesized that this criterion could be used as a predictor for responding to chemotherapy. Our results showed a significant higher level of MiR-551 in AML patients after chemotherapy, also patients who had aGVHD had insignificant higher expression of this MiR, which was in line with the aforementioned study, concluding poor prognosis and more relapse amongst those with the higher expression level of MiR-155b. AML classification and cytogenic subtypes based on MiR-155b were also considered in his study. We observed significantly higher expression level of MiR-551 in those with high risk AML in comparison with intermediate-risk patients, but no difference was detected between M3 and none-M3 patients[33]. Other studies also suggested that this MiR is oncogenesis and its higher expression level is associated with poor prognosis in many malignancies[16,34]. Another MiR, associated with leukemia is MiR-92b. Tanaka et al. proved that patients with acute leukemia have significantly lower expression level of this MiR, which was in agreement with our study, reporting lower expression level of MiR-92b in AML patients[16]. Although the expression of this MiR significantly increased after chemotherapy, higher expres-

sion level was observed amongst those who did not respond to chemotherapy. Some studies showed that up-regulation of MiR-92b promotes tumor growth, and its higher level was detected in malignancies suggesting it as a target for treatment[35-37]. In our earlier study, we have shown that MiR-92a and MiR-181a are upregulated in newly diagnosed AML patients. We also demonstrated for the first time that that c-Kit gene may be a novel target gene for MiR-92a and MiR-181a[22]. Also, we saw an insignificant increase of MiR-92b amongst those with high-grade GVHD. In our earlier study, we evaluated the expression of the MiR-181b and MiR-222 in AML patients and healthy controls and also an association with response to treatment and development of aGvHD[21]. It was also significantly higher in high-risk patients in comparison to those with intermediate risk. As for cytogenic abnormalities, with significant expression of MiR-92b in patients with FLT3 mutation and MLLT3 chromosome abnormalities, this MiR can be used as a classification indicator. To the best of our knowledge, this is the first plenary study on these three MiRs, specially MiR-1275 in AML patients. All in all, we suggest that MiR-1275-, MiR-551, MiR-92 can be used in diagnosis, classification and determination of response to chemotherapy and HSCT in AML patients, and can even become the target of therapy in the future.

Conclusion

Our results demonstrated that that MiR-1275-, MiR-551 and MiR-92 are associated with cytogenetics, molecular alterations, marrow morphology, and clinical outcomes in AML patients. Moreover, further cohort studies are warranted to determine whether manipulation of the altered microRNA can become a feasible therapeutic strategy as an addition to the modern armamentarium for “personalized” AML treatment.

Acknowledgment
The author would like to thank Shiraz University of Medical Science, also the Hematology Research Center. The authors wish to thank Mr. H. Argasi at the Research Consultation Center (RCC) of Shiraz University of Medical Sciences for his invaluable assistance in editing this manuscript.

Funding: This study was financially supported by Shiraz University of Medical Sciences [grant number 94-01-104-11279].

Conflict of interest statement: The authors declare that they have no conflicts of interest.

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