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Genetic Variants of MicroRNA-146a and MicroRNA-196a2 are Associated with Poor Outcome but not Risk of High-Grade B-Cell Non-Hodgkin Lymphoma

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Abstract

Background: Polymorphisms in microRNAs (miRNAs) encoding genes are involved in carcinogenesis. However, their relation to lymphomagenesis is still unclear.
Aim: To investigate the influence of miRNA-146a rs2910164 G/C polymorphism and miRNA-196a2 rs11614913 C/T polymorphism on risk and clinical outcome of high-grade B cell non-Hodgkin lymphoma (HGB-NHL).
Methods: Seventy-five patients with HGB-NHL and 100 matched controls were screened for miRNA-146a rs2910164 G/C and miRNA-196a2 rs11614913 C/T polymorphisms by Polymerase Chain Reaction-Restriction Fragment length Polymorphism (PCR-RFLP).
Results: The two studied miRNA polymorphisms were not associated with the risk of NHL. The GG genotype of miRNA-146a rs2910164 was associated with a worse disease-free survival (DFS) compared to the GC and CC genotypes (HR =5.7; 95% CI=1.05-31.09; p=0.044). The miRNA-196a2 rs11614913 CC genotype was associated as well with worse DFS compared to the CT and TT genotypes (HR=10.37; 95% CI=1.80-59.62; p = 0.009). No significant association was found between the studied miRNA polymorphisms and patients' overall survival.
Conclusions: miRNA-146a rs2910164 G/C and miRNA-196a2 rs11614913 C/T polymorphisms may be associated with shorter DFS in HGB-NHL.

Keywords: High-grade non-Hodgkin lymphoma, miRNA-146a rs2910164, miRNA-196a2 rs11614913, Prognosis

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Introduction

MicroRNAs (miRNAs) are endogenous short (21-24 nucleotides) single stranded non-protein coding RNA molecules that control gene expression at the posttranscriptional level [1]. They bind either to the 3'-untraslated end of their target messenger RNA (mRNA) with subsequent translational repression or to the open reading frame resulting in mRNA degradation [2]. Therefore, they are responsible of many physiological processes including cell proliferation, differentiation and apoptosis [3].

MiRNAs have specific expression patterns in different cancers and therefore they may be considered as non-invasive tumour markers for cancer diagnosis and prognosis [4]. Single nucleotide polymorphisms (SNPs) in genes coding miRNAs may disrupt their expression and maturation and might be implicated in the process of carcinogenesis [5]. MiRNA-146a rs2910164 G/C polymorphism and miRNA-196a2 rs11614913 C/T polymorphism have been found to be associated with susceptibility to a variety of solid tumours like colorectal cancer [6, 7], stomach cancer [8, 9], hepatocellular carcinoma [10, 11], breast cancer [12] and papillary thyroid carcinoma [13].

Little is known about the association between these miRNA gene polymorphisms and haematological malignancies like leukemia and lymphoma. B-cell non-Hodgkin lymphoma (B-NHL) is a genetically heterogeneous B-cell neoplasm in which molecular biomarkers have been widely used for diagnosis and prognosis [14]. Few studies have explored the association between miRNA-146a and miRNA-196a2 polymorphisms and NHL focusing mainly on disease susceptibility [15-17]. We performed this work to study the relation between miRNA-146a rs2910164 G/C polymorphism and miRNA-196a2 rs11614913 C/T polymorphism and risk of high-grade B-NHL and to identify their influence on disease outcome.

Methods

This single institution observational case-control study was conducted during the period from January 2017 through January 2019 at Kasr Al-Ainy School of Medicine, Cairo University, Egypt.

Participants

The study included 75 patients with high grade B-NHL and 100 age and sex matched healthy controls. Patients were enrolled in the study during their follow up visits at Kasr Al-Ainy Centre of Clinical Oncology and Nuclear Medicine (NEMROCK), Cairo University. Healthy controls were invited to participate in the study during their outpatient clinic visits at the New Kasr Al-Ainy Teaching Hospital for routine check-up provided that they have normal complete blood count.

Management of non-Hodgkin lymphoma

According to the world health organization (WHO) classification, the diagnosis and classification of NHL was based on histopathological examination and immunohistochemical (IHC) studies of lymph node biopsy [18]. Due to logistic reasons, BCL2 and c-myc were done in some patients by IHC to detect double expressor diffuse large B-cell lymphoma (DLBCL). All patients were evaluated by history and clinical examination. Laboratory work up included complete blood picture, renal and hepatic profile, serum uric acid, lactate dehydrogenase (LDH), bone marrow biopsy and screening for hepatitis B surface antigen. In addition to echocardiography, patients had computerized tomography (CT) with contrast of the chest, abdomen, and pelvis, positron emission tomography (PET/CT) was done if feasible. Clinical staging was assessed according to the Ann Arbor classification system [19] and performance status (PS) was determined using the Eastern Cooperative Oncology Group (ECOG) Scale [20]. The International Prognostic Index (IPI) score was used to classify patients into low, low-intermediate, high-intermediate or high risk groups [21]. Patients were assessed clinically before each treatment cycle, by CT scan or PET/CT after 3 cycles and at the end of treatment plan. Assessment of response was performed according to Lugano criteria [22].

Non-bulky early disease (stages I and II) received either R-CHOP (rituximab plus cyclophosphamide, doxorubicin, vincristine and prednisone) for 3 cycles and involved field radiotherapy or 6 cycles of R-CHOP, while patients with bulky disease receive 6 cycles of R-CHOP and radiotherapy. Patients with advanced disease (stages III and IV) received 6 cycles of R-CHOP. R-EPOCH (rituximab plus etoposide, prednisone, vincristine, cyclophosphamide and doxorubicin) regimen was used in patients with primary mediastinal large B-cell lymphoma and double expressor lymphoma.

Genetic study

Three mL of venous blood was collected on ethylene diamine tetra- acetic acid (EDTA) by sterile venepuncture using a sterile vacutainer tube. By using Gene JET Whole blood Genomic DNA purification Mini kit (Thermo Fisher Scientific, *USA*), genomic DNA was extracted from whole blood. Genotyping of miRNA-146a rs2910164 and miRNA-196a2 rs11614913 was performed by Polymerase Chain Reaction-Restriction Fragment length Polymorphism (PCR- RFLP) assay as described before [12]. The PCRs were done in a total volume of 25 µL containing 100 ng genomic DNA, 25 pM of each primer and 12.5 µL PCR master mix.

The PCR conditions comprised of an initial denaturation step at 94°C for 5 minutes followed by 30 cycles of denaturation at 94°C for 60 seconds, annealing at 62°C for miRNA-146a and 63°C for miRNA-196a2; for 60 seconds and extension at 72°C for 30 seconds and final extension at 72°C for 10 minutes. The presence of the PCR amplicon (147 bp for miRNA-146a and 149 bp for miRNA-196a2) was confirmed on 2% agarose gel electrophoresis. The PCR products were digested overnight at 37°C with the appropriate restriction enzyme (SacI for miRNA-146a and MspI for miRNA-196a2). Visualization of digested PCR products were performed on ethidium bromide stained 3% agarose gel electrophoresis.

Statistical analyses

Numerical data were presented as mean and standard deviation and compared by student's t test, while qualitative data were described as number and percentage and compared by Chi-square / Fisher's exact test. The SNP genotypes were grouped according to the dominant and recessive models. Disease-free survival (DFS) and overall survival (OS) were conducted using Kaplan-Meier method. DFS was calculated from date of complete remission till date of relapse. OS was calculated from the date of diagnosis to the date of death or the last follow up. Comparison between two survival curves was done using log rank test. Association between the genotypes of patients and survivals was estimated by univariate Cox regression analysis and results were expressed as hazard ratio (HR) with 95% confidence interval (CI). A p-value < 0.05 was considered significant.

Statistical analysis was performed using IBM SPSS® Statistics version 24 (IBM® Corp., Armonk, NY, USA).

Results

The study included 75 high grade B-NHL patients with a mean age of 48.89± 12.06 years. They were 32 males and 43 females. Clinicopathological characteristics of patients are shown in Table 1. The majority of patients (86.7%) were DLBCL. Other pathological subtypes include; 6 patients (8%) with T-cell rich B-cell lymphomas, 3 (4%) with mantle cell lymphomas and 1 (1.3%) with grade III follicular lymphoma. Based on their response to therapy, 61 (81.3%) patients achieved complete remission (CR), 1 (1.3%) showed partial remission (PR), 13 (17.3%) were refractory to therapy and 9 (12%) showed disease relapse during follow up.

Genotype and allele frequencies of miRNA-146a and miRNA-196a2 polymorphisms among patients and control groups are shown in Table 2.

Polymorphisms in miRNA-146a and miRNA-196a2 were not found to be associated with risk of high-grade B-NHL among the studied patients. Furthermore, no statistical differences were encountered when patients were stratified by histological subtype, B symptoms, bone marrow involvement, clinical stage, PS, IPI and LDH level (Tables 3 and 4).

At the time of analysis (June 2020), the estimated DFS was 92.5% at 1 year, and 71.4% at 3 years for a median follow up of 13.5 months. The GG genotype of miRNA-146a rs2910164 was associated with a worse DFS compared to the GC and CC genotypes (HR =5.7; 95% CI=1.05-31.09; p=0.044) in the recessive model (GG vs GC/CC) (Figure 1, Table 5).

Likewise, the miRNA-196a2 rs11614913 CC genotype was associated with worse DFS compared to the CT and TT genotypes (HR=10.37; 95% CI=1.80-59.62; p = 0.009) in the recessive model (CC vs CT/TT), (Figure 2, Table 5). The estimated OS at 1 year was 91% and at 3 years was 70%. No statistically significant difference was demonstrated between miRNA-146a and miRNA-196a2 genotypes and OS among the studied patients (Table 6).

Table 1: Characteristics of 75 patients with non-Hodgkin lymphoma

Characteristic	*n* (%)
Histological subtype	
DLBCL	65 (86.7)
Others	10 (13.3)
B symptoms	
Yes	43 (57.3)
No	32 (42.7)
Bone marrow involvement	
Yes	17 (22.7)
No	58 (77.3)
Clinical stage	
Early (I/II)	33 (44)
Late (III/IV)	42 (56)
ECOG performance status	
<2	49 (65.3)
≥ 2	26 (34.7)
IPI risk group	
Low / Low-intermediate	50 (66.7)
High-intermediate / High	25 (33.3)
Lactate dehydrogenase	
Normal	14 (18.7)
Elevated	61 (81.3)

DLBCL: Diffuse large B-cell lymphoma, **ECOG:** Eastern Cooperative Oncology Group, **IPI:** International Prognostic Index

Table 2: Genotype and allele frequencies of miRNA-146a and miRNA-196a2 in patients with B-NHL and control subjects

	Patients (*n*=75), *n* (%)	Controls (*n*=100), *n* (%)	*p* value
miRNA-146a			
Genotypes			
GG	27 (36)	32 (32)	0.498
GC	39 (52)	60 (60)	
CC	9 (12)	8 (8)	
Alleles			
Allele G	93 (62)	124 (62)	1
Allele C	57 (38)	76 (38)	
Recessive model			
GG	27 (36)	32 (32)	0.629
GC & CC	48 (64)	68 (68)	
Dominant model			
GG & GC	66 (88)	92 (92)	0.443
CC	9 (12)	8 (8)	
miRNA-196a2			
Genotypes			
CC	30 (40)	36 (36)	0.153
CT	34 (45.3)	57 (57)	
TT	11 (14.7)	7 (7)	
Alleles			
Allele C	94 (62.7)	129 (64.5)	0.73
Allele T	56 (37.3)	71 (35.5)	
Recessive model			
CC	30 (40)	36 (36)	0.637
CT & TT	45 (60)	64 (64)	
Dominant model			
CC & CT	64 (85.3)	93 (93)	0.131
TT	11 (14.7)	7 (7)	

Discussion

Growing evidence revealed the association between SNP in genes encoding miRNA and susceptibility of different types of cancer particularly stomach, colorectal and breast cancers. MiRNAs that are frequently associated with cancers are: miRNA-146a, miRNA-196a-2 and miRNA-149 [5]. Some miRNA genes polymorphisms were linked to poor disease outcome like worse overall survival of patients with stomach and lung cancers [23], high rate of recurrence in colorectal adenocarcinoma patients [24] and unfavourable recurrence free survival in Chinese patients with colorectal cancer [25].

Few data are available about the association between miRNA gene polymorphisms and NHL. The present study investigated the association between miRNA-146a rs2910164 G/C polymorphism and miRNA-196a2 rs11614913 C/T polymorphisms and susceptibility and outcome of high-grade B-NHL among Egyptian patients. We found that polymorphisms in miRNA-146a and miRNA-196a2 were not associated with risk of high-grade B-NHL. In agreement with our study, these polymorphisms were not associated with susceptibility to acquired immune deficiency syndrome (AIDS) associated NHL in a previous multicentre study [17]. In contrast to our findings, the CC genotype of miRNA-146a rs2910164 polymorphism was found to be associated with risk of DLBCL in Chinese Han population [15]. Likewise, the CC/CT genotypes of miRNA-196a2 were associated with lymphoma risk in a cohort of B/T-NHL patients of Chinese Han origin [16].

As for disease outcome, our results show for the first time an association between the GG genotype of miRNA-146a rs2910164 and the CC genotype of miRNA-196a2 rs11614913 and worse DFS. A systematic review and meta-analysis investigated the prognostic role of miRNA polymorphisms in cancers other than NHL showed that the CC genotype of miRNA-196a2 rs11614913 is associated with a worse DFS. However, the GG genotype of miRNA-146a rs2910164 is associated with better DFS [26]. These results were contrary to our results regarding miRNA-146a polymorphism but consistent with our findings for miRNA-196a2 polymorphism. Similar results were observed for OS (but not DFS) in another meta-analysis that also did not include NHL studies [23]. This discrepancy may be the result of different types of cancers studied and different populations included (most of them are Asian). The expression level of miRNAs is not the same in cancer and normal cells and even it varies among different types of cancer [4]. This may explain the role of SNPs in genes coding miRNAs in cancer pathogenesis.

Table 3: The relationship between miRNA-146a polymorphism and the clinicopathological characteristics of patients

Characteristic	GG (*n*=27)	GC & CC (*n*=48)	*p* value	CC (*n*=9)	GC & GG (*n*=66)	*p* value
	n (%)			*n* (%)		
Histological subtype						
DLBCL	24 (88.9)	41 (85.4)	1	8 (88.9)	57 (86.4)	1
Others	3 (11.1)	7 (14.6)		1 (11.1)	9 (13.6)	
B symptoms						
Yes	18 (66.7)	25 (47.9)	0.237	8 (88.9)	35 (53)	0.069
No	9 (33.3)	23 (52.1)		1 (11.1)	31 (47.0)	
Bone marrow involvement						
Yes	5 (18.5)	12 (25)	0.579	3 (33.3)	14 (21.2)	0.674
No	22 (81.5)	36 (75)		6 (66.7)	52 (78.8)	
Clinical stage						
Early (I / II)	13 (48.1)	20 (41.7)	0.634	3 (33.3)	30 (45.5)	0.723
Late (III/IV)	14 (51.9)	28 (58.3)		6 (66.7)	36 (54.5)	
ECOG performance status						
<2	18 (66.7)	31 (64.6)	1	4 (44.4)	45 (68.2)	0.261
≥ 2	9 (33.3)	17 (35.4)		5 (55.6)	21 (31.8)	
IPI risk group						
Low / Low-intermediate	17 (63)	33 (68.8)	0.799	4 (44.4)	46 (69.7)	0.261
High-intermediate / High	10 (17.0)	15 (31.2)		5 (55.6)	20 (30.3)	
Lactate dehydrogenase						
Normal	5 (18.5)	9 (18.8)	1	2 (22.2)	12 (18.2)	1
Elevated	22 (81.5)	39 (81.2)		7 (77.8)	54 (81.8)	

DLBCL: Diffuse large B-cell lymphoma, **ECOG:** Eastern Cooperative Oncology Group, **IPI:** International prognostic index

Table 4: The relationship between miRNA-196a2 polymorphism and the clinicopathological characteristics of patients

Characteristic	CC (*n*=30)	CT & TT (*n*=45)	*p* value	TT (*n*=11)	CT & CC (*n*=64)	*p* value
	n (%)			*n* (%)		
Histological subtype						
DLBCL	25 (83.3)	40 (88.9)	0.508	10 (90.9)	55 (85.9)	1
Others	5 (16.7)	5 (33.3)		1 (9.1)	9 (14.1)	
B symptoms						
Yes	15 (50)	28 (62.2)	0.345	8 (72.7)	35 (54.7)	0.335
No	15 (50)	17 (37.8)		3 (27.3)	29 (45.3)	
Bone marrow involvement						
Yes	5 (16.7)	12 (26.7)	0.403	4 (36.4)	13 (20.3)	0.257
No	25 (83.3)	33 (73.3)		7 (63.6)	51 (79.7)	
Clinical stage						
Early (I / II)	11 (36.7)	22 (48.9)	0.347	5 (45.5)	28 (43.8)	1
Late (III/IV)	19 (63.3)	23 (51.1)		6 (54.5)	36 (56.2)	
ECOG performance status						
<2	22 (73.3)	27 (60)	0.323	5 (45.5)	44 (68.8)	0.174
≥2	8 (26.7)	18 (40)		6 (54.5)	20 (31.2)	
IPI risk group						
Low / Low-intermediate	19 (63.3)	31 (73.4)	0.803	5 (45.5)	45 (70.3)	0.164
High-intermediate / High	11 (36.7)	14 (26.6)		6 (54.5)	19 (29.7)	
Lactate dehydrogenase						
Normal	5 (16.7)	9 (20)	0.772	0	14 (21.9)	0.112
Elevated	25 (83.3)	36 (80.0)		11 (100)	50 (78.1)	

DLBCL: Diffuse large B-cell lymphoma, **ECOG:** Eastern Cooperative Oncology Group, **IPI:** International prognostic index

Table 5: Relationship between miRNA-146a and miRNA-196a2 polymorphisms and disease-free survival

Polymorphisms		No. of patients	No. of relapses	Cumulative survival (%)		*p* value
				At 12 months	At 36 months	
miRNA-146a	**GG**	23	4	90.9	72.7	0.044
	GC & CC	38	5	93.5	71.7	
miRNA-146a	**GG & GC**	54	9	91.7	68.9	0.395
	CC	7	0	100	NR	
miRNA-196a2	**CC**	24	5	88	NR	0.009
	CT & TT	37	4	96.3	88.3	
miRNA-196a2	**CC & CT**	51	8	93.9	70.9	0.659
	TT	10	1	83.3	83.3	

NR: Not reached

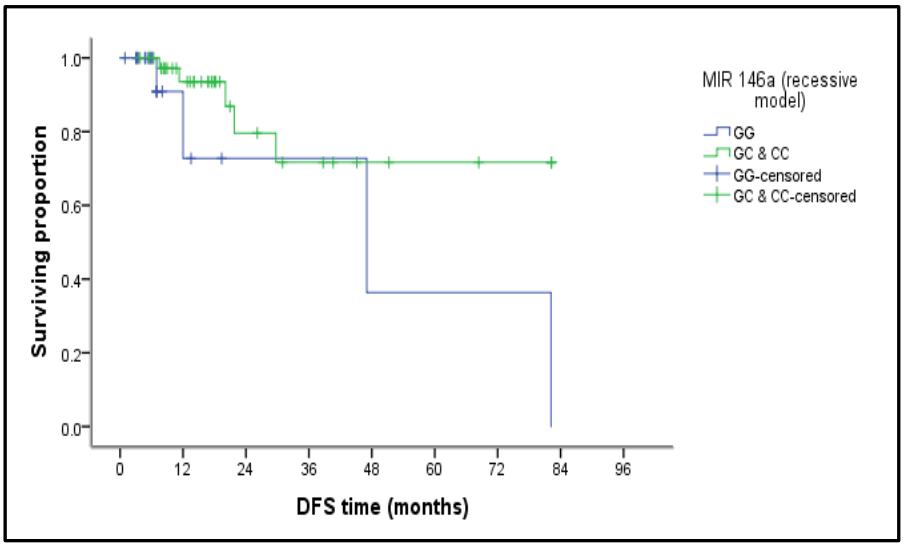

Figure 1: Kaplan–Meier curves for disease-free survival (DFS) according to miRNA-146a rs2910164 genotypes

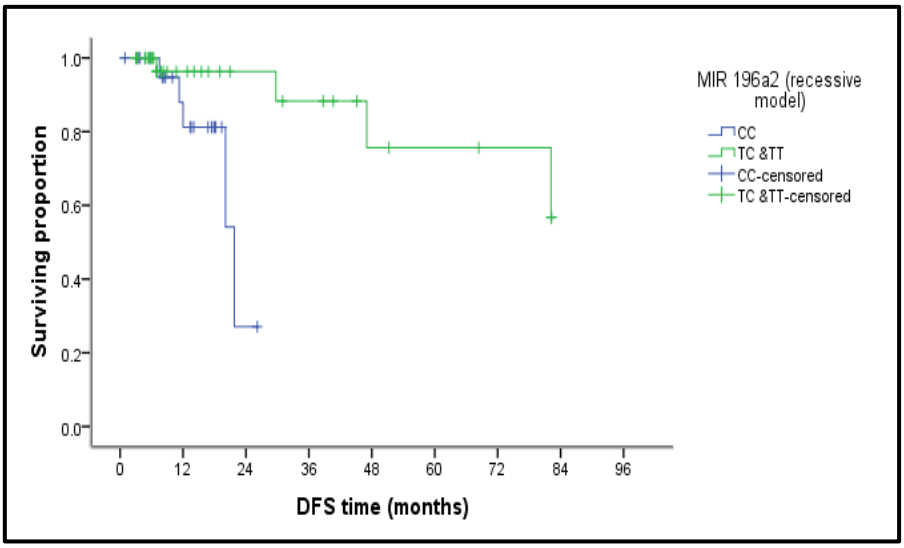

Figure 2: Kaplan–Meier curves for disease-free survival (DFS) according to miRNA-196a2 rs11614913 genotypes

Table 6: Relationship between miRNA-146a and miRNA-196a2 polymorphisms and overall survival

Polymorphisms		No. of patients	No. of events	Cumulative survival (%)		*p* value
				At 12 months	At 36 months	
miRNA-146a	**GG**	27	3	93.5	77.9	0.152
	GC & CC	48	1	97.5	97.5	
miRNA-146a	**GG & GC**	66	3	96.8	91.9	0.319
	CC	9	1	88.9	88.9	
miRNA-196a2	**CC**	30	1	83.3	83.3	0.587
	CT & TT	45	3	92.9	92.9	
miRNA-196a2	**CC & CT**	64	3	96.7	91.9	0.356
	TT	11	1	90	90	

The G allele of miRNA-146a rs2910164 was found to be associated with increased miRNA-146a expression [13]. Upregulation of miRNA-146a was detected in DLBCL cases suggesting a role of this polymorphism in pathogenesis of DLBCL [15]. The CC/CT genotypes of miRNA-196a2 rs11614913 were found to be associated with indictors of poor NHL prognosis like advanced stage, bone marrow invasion, and B symptoms. This was attributed to higher expression of miRNA-196a2 that was detected among patients carrying the C allele of miRNA-196a2 rs11614913 [16].

Conclusions

The results of the current study provide initial evidence that miRNA-146a and miRNA-196a2 polymorphisms may have a negative impact on NHL prognosis. Further larger scale studies are warranted to validate our findings.

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Not applicable.

Authors' contribution

Conception or design: SMM, HS, SK, WE; Acquisition, analysis or interpretation of data: DSM, SMM, WE; Drafting or revising the manuscript: SMM, HS, SK, DSM, WE; Approval of the manuscript version to be published: All authors; Agreement to be accountable for all aspects of the work: All authors.

Conflict of interest

The authors declare that they have no conflict of interest to disclose.

Data availability

The deidentified datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Ethical considerations

The study was approved by the Research Committees of Kasr Al-Ainy Center of Clinical Oncology and Nuclear Medicine and the Clinical and Chemical Pathology Department, Faculty of Medicine, Cairo University.

Patients and controls signed an informed consent before beginning of the study.

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Study registration

Not applicable.

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