miRNAs as indices predicting early toxicity in high-dose melphalan chemotherapy followed by autologous stem cell support in multiple myeloma patients

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Abstract

We present a pivotal study of miRNAs as indices predicting early organ toxicity in multiple myeloma patients. Exposure to high-dose melphalan results in increased concentration of miR-210-5p and down-regulation of miR-122-5p. Further studies are needed to confirm the findings.

Background

High-Dose Melphalan chemotherapy (HD-Mel) and autologous stem cell transplantation (ASCT) is the treatment of choice for younger patients with Multiple Myeloma (MM). The procedure is safe with 1.75% treatment related mortality. Toxicity is primarily due to mucositis, infections and diarrhoea. Some patients may develop grade 1-4 organ toxicity (liver 22.8%, renal 6.1% and cardiac 5.3%) according to Common Toxicity Criteria version 4.0 (1).

Circulating microRNAs (miRNAs) have been reported to play a role in many pathological conditions including cancers (2). It is also known that miRNAs have diagnostic utility in identifying organ impairment (e.g. liver, kidney, heart) (3,4,5).

According to published data on profiling miRNAs production, we chose five types of those molecules, highly selective after tissue damage and presented in serum. Three of them (miR-423-5p, miR-208a-3p, miR-499-5p) are specific to myocardium tissue damage. The latter two, involved in hepato- and nephrotoxicity, are miR122-5p, miR-210-5p respectively.

Objective

The study is designed to assess the role of selective miRNAs as markers of early toxicity after HD-Mel treatment followed by ASCT in MM patients.

Materials & Methods

15 patients with MM (7 males, 8 females) were admitted to the Transplant Unit at Wrocław Medical University between Nov. 2016 and May 2017. Patients with amyloidosis were excluded. 5 healthy volunteers represented a comparator group. The average age was 53.2 years (range 54-67).

Blood samples were collected before chemotherapy (I) and on the first (II) and eighth day (III) after HD-Mel treatment to evaluate the concentration of miR-423-5p, miR-208a-3p, miR-499-5p, miR-210-5p, miR-122-5p as well as creatine, aspartate and alanine aminotransferases, CK-MB mass, hsTroponin I and BNP.

Blood samples were collected into RNA later solution tubes (Qiagen, Hilden, Germany) and stored at -70°C for Digital Droplet PCR experiments. Biochemistry results were obtained directly after collection at a local laboratory. Statistical analysis was performed using Statistica software version 13.1.

Results

correlations	I	II	III
miR423-5p vs creatinine	-0,17	-0,55	-0,04
miR208a-3p vs CK-MB	-0,50 (p=0,057)	0,08	-0,22
miR499-5p vs creatinine	-0,18	-0,57	-0,09
miR210-5p vs creatinine	-0,21	-0,58	0,16
miR122-5p vs AST	0,36	0,24	0,55 (p=0,099)
miR-122-5p vs ALT	0,17	-0,09	0,59
miR-122-5p vs creatinine	0,09	-0,57	-0,09

Tab. 1. Spearman rank correlations between miRs and biochemistry parameters in blood samples for I, II, III collections (bold font for p < 0.05)

Results

Ryc. 1. Concentrations of of miR-423-5p, miR-208a-3p, miR-499-5p, miR-210-5p, miR-122-5p in the blood of patients before chemotherapy (I) and on the first (II) and eighth days (III) after HD-Mel treatment

Discussion

miR-122-5p presents positive correlation with AST (R=0,55, p=0,099). The process was also observed for Viral-, Alcohol- and Chemical-related Hepatic Diseases (3). After HD-MEL we observed slight hepatotoxicity (only grade 1-4%), which indicates that miR-122-5p is a very sensitive hepatic biomarker. These findings need to be explored with more types of hepatotoxic chemotherapy regimens (e.g. BEAM, HD-MTX). miR-208a-3p is known as an acute myocardial infarction biomarker. In our study its concentration was stable and not significantly different than in the control group. However, we did not observe any cardiac complications during ASCT. Nevertheless, miR-122-5p presents negative correlation with CK-MB mass in MM patients before HD-MEL (R=-0.50, p=0,057). The concentration of selective renal biomarker miR-210-5p increased in the first day after HD-MEL, but correlation with creatinine was not observed.

Summary

In our study cardiac biomarkers were poorly correlated with standard biochemical tests. It is worth to explore miR-122-5p as a sensitive hepatic biomarker. miR-210-5p rises after HD-MEL exposure. The study is ongoing and all existing results will be confirmed with a larger group of patients.

References

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