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Содержание:

ბათა საერთო მოცულობა შედგენდა 800–მდე მოსწავლეს. სკრინინგული კვლევა მოიცავდა სპეციალისტების მულტიდისციპლინური ჯგუფის კონსულტაციებს, დიაგნოზის დაზუსტების მიზნით – დამატებით ლაბორატორიულ და ინსტრუმენტულ კვლევებს. ჩატარებული კვლევის შედეგად გამოვლინდა, რომ პრაქტიკულად ჯანმრთელი იყო გამოკვლეული კონტინგენტის 28.3%, ფუნქციური დარღვევები აღენიშნებოდა 55%–ს, ხოლო ქრონიკული დაავადებები – 16.7%–ს. როგორც ქალაქის, ისე სოფლის არეალში პრევალირებდა საჭმლის მომნელებელი სისტემის, სისხლისა და სისხლწარმომქმნელი ორგანოების,ნერვული სისტემის,ოფთალმოლოგიური პათოლოგიისა და საყრდენ–მამოძრავებელი აპარატის დაავადებათა ხვედრითი წილი.

GALECTIN-3 AS A PREDICTOR OF STATIN TREATMENT EFFICACY IN PATIENTS WITH MULTIPLE MYELOMA

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Endothelial damage and perivascular plasma cells infiltrates are vital in the development of multiple myeloma. Recent studies have found that endothelial dysfunction might be result in multiple myeloma progression and adverse effects of drug implementation [3]. On the other hand, there is a direct correlation between microvessel density in multiple myeloma and parameters of disease progression [12].

Galectins are a family of lectin molecules that have emerged as key players in inflammation and tumor progression by displaying intracellular and extracellular activities [6]. Galectin-3 (Gal-3) has been found to be involved in many biological processes, such as cell-cell and cell-extracellular matrix adhesion, cell growth and differentiation, the cell cycle, signaling, apoptosis and angiogenesis. Consequently, Gal-3 is involved in the regulation of development, immune reactions, tumorigenesis, tumor growth and metastasis [8].

It is now well recognized that interactions between tumor cells and stromal cells in the tumor microenvironment play a determinant role in cancer initiation and progression [14]. The production of soluble growth factors, cytokines and chemokines by stromal cells in the presence of tumor cells is one among the several mechanisms by which the tumor microenvironment affects cancer cells [9]. Among these soluble factors is interleukin-6 (IL-6) that promotes the self-seeding of circulating tumor cells and contributes to a stress response that protects tumor cells from drug action [11]. It was reported that the production of Gal-3 binding protein by tumor cells was one mechanism that stimulated the expression of IL-6 in bone marrow mesenchymal stem cells and in monocytes/macrophages [4].

Moreover, elevated Gal-3 associates with increased cardiovascular risk [7,10]. In response to acute and chronic damage, the immune cells recruit to the cardiomyocytes, with the production of cell-signaling proteins and the activation of fibroblasts and myofibroblasts, which lead to the deposition of procollagen into the extracellular matrix and cardiac fibrosis [2]. The up-regulation of myocardial Gal-3 has been demonstrated in a rat model of heart failure prone hypertensive hearts [13], interferon 6-induced murine chronic active myocarditis and cardiomyopathy, and rat angiotensin II-induced hypertension. This up-regulation was associated with the concomitant activation of macrophages. Gal-3 has also been found to be significantly up-regulated in the hypertrophied hearts of patients with aortic stenosis and in the plasma of patients with acute and chronic heart failure. Numerous experimental studies have shown the important role of Gal-3 in cardiac remodeling due to fibrosis, independent of the fibrosis etiology. Some clinical studies have confirmed the predictive value of Gal-3 in all-cause mortality in patients with heart failure.

In our study, we aim to analyze the role of Gal-3 in the development of cardiovascular events, its value in screening and clinical decision making and its possible predictive application in follow-up as a “routine” test in an addition to established biomarkers, such as N-terminal pro-brain natriuretic protein (NT-proBNP).

In this context there is possibility to use statins in dyslipidemic patients with regression of multiple myeloma to prevent unfavorable cardiovascular outcomes under control of Gal-3 level.

The aim of the study: to investigate an interrelationship between pre-treatment Gal-3 level and one-year survival rate, cardiovascular events in subjects with multiple myeloma.

Material and methods. Eighty nine out subjects with full or partial remission of multiple myeloma were enrolled in the study. All subjects gave their written informed consent to participation in the study. Diagnosis and staging of multiple myeloma were defined by current clinical practice guidelines [1]. To be achieving remission chemotherapy was used accordingly contemporary clinical guidelines. All subjects were at full or partial remission stage at baseline. Patients were divided into 2 groups based on whether or not statins were included in their treatment: a statin group (n=43) and no statin group (n=46). Only patients with dyslipidemia were treated with statins. None of the patients had received any lipid-modulating medications, including statins or fibrates, before enrollment. Of the 43 patients in the statin group, 31 patients received 20-mg/day atorvastatin and 12 patients received 40-mg/day atorvastatin.

Echocardiography in B-mode was performed accordingly to Recommendation of American Society of Echocardiography on the scanner "MyLab 50" (Italy) using a transducer with a frequency of 2.5-3.5 MHz. End-diastolic and end-systolic LV volumes were obtained using a two-dimensional reference sector according to Simpson's method, and LV ejection fraction (LVEF) was calculated by accordingly conventional methods [5].

All blood samples were collected after fasting in cooling vacutainer and after that it was immediately centrifuged (4°C for 6.000 × 15 min). After centrifugation serum was blind coded and stored at -70° until used. Human Gal-3, IL-6 and NTproBNP were measured by ELISA technique (ELISA kits manufactured by R&G, United Kingdom) used for examination. All determinations were done by duplicating. Fasting plasma glucose (FPG) was quantified by the glucose oxidase procedure; HbA1c was measured by ion-exchange high-performance liquid chromatography (HPLC; Bio-Rad, Hercules, CA, USA).

Concentrations of total cholesterol (TC), low density lipoprotein (LDL) cholesterol and high density lipoprotein (HDL) cholesterol were determined by direct enzymatic methods using Dimension Clinical Chemistry System (Dade Behring Inc, Newark, NJ).

Clinical Events: Screening and Diagnostics
Clinical interviews were carried out every month for three years after baseline. The following are the clinical events verified: newly diagnosed strokes or TIAs; death for any reasons and sudden cardiac death; coronary ischemic events (myocardial infarction, unstable angina) that needed hospital admission for cardiovascular reasons, new-onset chronic heart failure. Newly diagnosed strokes were confirmed with CT. All clinical events were presented as cumulative.

All statistical analyses were performed in SPSS for Windows v. 17.0 (SPSS Inc., Chicago, IL, USA). All values were given as mean and 95% confidence interval [CI] or median and percentiles. An independent group t-test was used for comparisons for all interval parameters meeting the criteria of normality and homogeneity of variance. For interval parameters not meeting these criteria, the non-paramentric Mann-Whitney test was used to make comparisons between the groups. Comparisons of categorical variables between the groups were performed using the Chi2 test, and the Fisher exact test. The potential factors that may be associated with cardiovascular events was identified first by the univariate analysis, then multivariate logistic regression analyses were used to identify the predict factors. A calculated difference of $P<0.05$ was considered significant.

Results and their discussion. The baseline characteristic of both cohorts of the patients depending treatment regime is presented in the Table 1. All patients were matched accordingly age, sex, cardiovascular events, diabetes presentation rate, serum biomarker concentration, and concomitant medications.

All of the patients in the statin group tolerated the treatment well, and no serious side-effects were reported during the follow-up period. The effect of both statin regimes is reported in the Table 2. One can see, lipid lowering effect in statin user was associates with declined serum Gal-3 level, whereas in not statin users similar response was not appeared. No any changes in hemodynamics and other biomarkers between both cohorts were found.

Ninety two cumulative clinical events occurred in 36 patients (40,5%) within the follow-up, with their distribution being as follows: 8 cardiovascular deaths, 46 cardiac arrhythmias, 8 cardiac ischemic events, 2 strokes, 8 chronic heart failures and 22 hospital admissions for cardiovascular reasons.

Table 3 is reported characteristics of the multiple myeloma patients with vs without cardiovascular events. One can see, free-events subjects had lover levels of Gal-3, IL-6 and NT-proBNP than subjects with cardiovascular events. The data suggested that Gal-3 plasma levels were directly related to NT-pro-BNP ($r = 0.52$, $P = 0.009$). No relations were found in Gal-3 and IL-6.

Table 1. Baseline Clinical Characteristics

Variables	Statin users (n=43)	Never Statin users (n=46)	P-value
Age, years	59.09±8.10	59.78±9.02	0.71
Males, n (%)	15 (34.9)	25 (54.4)	0.07
Hypertension, n (%)	6 (14.0)	9 (19.6)	0.49
T2DM, n (%)	3 (7.0)	1 (2.2)	0.58
BMI, kg/m^2	27.67±4.55	26.30±3.51	0.11
Obesity, n (%)	7 (16.3)	3 (6.5)	0.15
Overweight, n (%)	14 (32.6)	13(28.3)	0.67
Adherence to smoking, n (%)	1 (2.2)	3 (7.0)	0.35
GFR, mL/min/1.73 m^2	100.26±21.51	102.75±19.89	0.57
HbA1c, %	5.15±0.79	5.04±0.70	0.50
Fasting blood glucose, mmol/L	7.78±0.67	4.60±0.58	0.18
Creatinine, μmol/L	70.42±15.85	70.22±12.62	0.95
Gal-3, ng/ml	10.48±9.54	11.76±40.41	0.98
NT-pro-BNP, pg /mL	11.50±10.40	12.23±13.38	0.758
IL-6, pg/ml	2.27±1.76	2.22±2.18	0.76
ACEI or ARAs, n (%)	8 (18.6)	11 (23.9)	0.55
Acetylsalicylic acid or clopidogrel, n (%)	36 (88.4)	38 (82.7)	0.89
Metformin, n (%)	2 (4.7)	1 (2.2)	0.53
Loop diuretics, n (%)	6 (14.0)	8 (17.4)	0.67
Mineralcorticoid receptor antagonists, n (%)	7 (16.3)	5 (10.9)	0.46

*note: * - statistically differences between parameters in the two groups (P<0.05); CI – confidence interval; T2DM – type two diabetes mellitus, GFR - Glomerular filtration rate, BMI - Body mass index, BNP – brain natriuretic peptide, ACEI – angiotensin-converting enzyme inhibitor, ARAs – angiotensin-2 receptors antagonists*

Table 2. Change in Clinical Characteristics According to Statin Treatment

Variables	Statin users (n=43)			Never Statin users (n=46)		
	Baseline	At 12 months (% change)	P-value	Baseline	At 12 months (% change)	P-value
Total cholesterol, mmol/L	5.18±0.96	4.41±0.98	<0.001	4.88±0.59	4.88±0.59	0.00 93
LDL-C, mmol/L	3.07±1.03	2.33±0.79	<0.001	2.78±0.52	2.81±0.61	0.77 9
HDL-C, mmol/L	1.47±0.37	1.45±0.38	0.06	1.53±0.32	1.45±0.34	0.91 8
Systolic BP, mm Hg	125.44±13.25	122.29±10.20	0.133	126.24±13.44	125.34±12.35	0.76 9
Heart rate, beats per 1 min.	80.28±9.6 7	75.04±20. 47	0.109	80.09±8.9 8	77.79±13. 07	0.22 5
LVEF, %	57.67±4.5 8	58.29±5.4 7	0.494	57.04±4.2 7	55.60±6.3 3	0.03 9
E/Am, U	1.12±0.24	1.11±0.25	0.965	1.20±0.24	1.10±0.24	0.08 6
E/Em, U	6.84±1.60	6.29±1.83	0.106	8.16±2.12	8.98±2.08	0.02 7
Gal-3, ng/mL	10.48±9.5 4	-6.2±0.23	0.05	11.76±40. 41	-2.1±0.26	0.86
NT-pro-BNP, pg /mL	11.50±10. 40	-3.1±0.12	0.88	12.23±13. 38	-2.9±0.15	0.92
IL-6, pg/mL	2.27±1.76	-7.6±0.17	0.04	2.22±2.18	-5.2±0.15	0.14

Table 3. Characteristics of the multiple myeloma patients with vs without CV events

Variables	Free-events subjects (n=53)	Subjects with CV events (n=36)	P-value
Age, years	59±8.57	61±8.35	0.61
Males, n (%)	19 (35.9)	21 (58.3)	0.37
Hypertension, n (%)	7 (13.2)	12 (22.2)	0.29
Dyslipidemia, n (%)	12 (22.6)	6 (16.7)	0.43
T2DM, n (%)	3 (5.1)	1 (2.7)	0.47
BMI, kg/m^2	26.74 (25.69-27.79)	27.40 (25.82-28.98)	0.55
Obesity, n (%)	7 (13.2)	3 (8.3)	0.62
Overweight, n (%)	18 (40.0)	9 (25.0)	0.55
Adherence to smoking, n (%)	1 (1.9)	4 (11.1)	0.61
GFR, mL/min/1.73 m^2	101.30±20.97	102.00±20.22	0.63
HbA1c, %	5.01±0.67	5.27±0.85	0.18
Fasting blood glucose, mmol/L	4.63±0.57	4.8±0.73	0.40
Creatinine, μmol/L	68.71±13.23	73.67±15.61	0.11
Total cholesterol, mmol/L	5.09±0,85	4.77±1.01	0.17
LDL-C, mmol/L	2.94±0,84	2.89±0.79	0.25
HDL-C, mmol/L	1.50±0,32	1.50±0.39	0.33
Gal-3, ng/ml	5.17 (2.87-7.48)	17.57 (11.36-23.79)	<0.001
NT-pro-BNP, pg /mL	5.68±6,34	23.8±18.47	0,004
IL-6, pg/ml	1.80±6.34	2.95±6.34	0.32
Systolic BP, mm Hg	124.3±12.71	129.0±14.02	0.5
Heart rate, beats per 1 min.	80.56±8.63	79.43±10.51	0.87
LVEF, %	58.11±4.18	55.84±4.52	0.60
E/Am, U	1.12±0.28	1.17±0.22	0.08
E/Em, U	7.14±1.71	8.29±2.30	0.03

*note: * - statistically differences between parameters in the two groups (P<0.05); CI – confidence interval; T2DM – type two diabetes mellitus, GFR - Glomerular filtration rate, HDL-C - high-density lipoprotein cholesterol, LDL-C - Low-density lipoprotein cholesterol, BP – blood pressure, BMI - Body mass index, BNP – brain natriuretic peptide, LVEF - Left ventricular ejection fraction, U – unit, Em - early diastolic myocardial velocity, Am - late diastolic myocardial velocity, E – peak velocity of early diastolic left ventricular filling*

Univariate logistic regression had exhibited that Gal-3 (odds ratio [OR]=1.17; 95% CI=1.04–1.29; P=0.002), NT-proBNP (OR = 1.04; 95% CI 1.02–1.10; P < 0.05) and statin therapy (OR=1.07; 95% CI = 1.02–1.11; P = 0.001) predicted one-year cumulative CV events. After adjustment on statin therapy, Gal-3 remained independent predictor one-year cumulative cardiovascular events (OR = 1.08; 95% CI = 1.06–1.11; P = 0.001). When initial serum Gal-3 level has incorporated into prediction model, statin therapy was found as predictor for improving survival in patients with elevated serum Gal-3 level (>14 ng/ml). The results of the study have confirmed an assumption regarding statins' positive effect on survival in higher risk subjects with multiple myeloma. Although this is a preliminary result, probably, it is required more investigations to explain the role of pretreatment level of Gal-3 as independent predictor of long-term clinical outcomes in stable individuals with multiple myeloma.

Conclusions. Gal-3 has a high predictive value in terms of prognosis and an additive value to natriuretic peptide measurement. The results of the study have exhibited that elevated pre-treatment Gal-3 level might be a powerful predictor of positive effect of statins on survival in patients with chronic lymphocytic leukemia.

Complementary prospective studies are still needed to confirm its prognostic value and to determine the target population for combined biomarker analysis and, maybe in the future, for using Gal-3 as a target for preventive treatment of cardiovascular events in patients with multiple myeloma.

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SUMMARY

GALECTIN-3 AS A PREDICTOR OF STATIN TREATMENT EFFICACY IN PATIENTS WITH MULTIPLE MYELOMA

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The aim of the study: to investigate an interrelationship between pre-treatment galcetin-3 (Gal-3) level and one-year survival rate, cardiovascular events in subjects with multiple myeloma.

Eighty nine subjects with full or partial remission of multiple myeloma were enrolled in the study. Patients were divided into 2 groups based on whether or not statins were included in their treatment: a statin group (n=43) and a no statin group (n=46). Among the 43 patients in the statin group, 31 patients received 20mg/day atorvastatin and 12 patients received 40-mg/day atorvastatin. None of the patients had received any lipid-modulating medications, including statins or fibrates, before enrollment. Observation period was up to 1 year. Blood samples for biomarkers measurements were collected. ELISA method for measurements of circulating level of galectin-3, interleukin-6 and NT-pro-brain natriuretic peptide were used.

Lipid lowering effect in statin user was associates with declined serum Gal-3 level, whereas in not statin users similar response was not appeared. No any changes in hemodynamics and other biomarkers between both cohorts were found. Univariate logistic regression had exhibited that galtctin-3 (odds ratio [OR] = 1.17; 95% CI = 1.07–1.29; P = 0.002), NT-pro-brain natriuretic peptide (OR=1.04; 95% CI=1.02–1.10; P<0.05) and statin therapy (OR=1.07; 95% CI = 1.02–1.11; P = 0.001) predicted one-year cumulative CV events. After adjustment on statin therapy, galectin-3 remained independent predictor one-year cumulative cardiovascular events (OR=1.08; 95% CI=1.06–1.11; P=0.001). When initial serum galectin-3 level has incorporated into prediction model, statin therapy was found as predictor for improving survival in multiple myeloma patients with elevated serum galectin-3 level (>14 ng/ml).

Elevated pre-treatment galectin-3 level was found a powerful predictor of positive effect of statins on survival in patients with regression of multiple myeloma.

Keywords: galectin-3, interleukin-6, NT-pro-brain natriuretic peptide, multiple myeloma, statin, survival, prognosis.

РЕЗЮМЕ

ГАЛЕКТИН-3 КАК ПРЕДИКТОР ЭФФЕКТИВНОСТИ ЛЕЧЕНИЯ СТАТИНАМИ У ПАЦИЕНТОВ С МНОЖЕСТВЕННОЙ МИЕЛОМОЙ

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Целью исследования явилось определение взаимосвязи между уровнем галектина-3 до лечения, кардиоваскулярными событиями и коэффициентом годичной выживаемости у пациентов с множественной миеломой.

Исследованы 89 пациентов с регрессией множественной миеломы. Пациенты в зависимости от наличия статинов в их лечении разделены на две группы: группа, получавшая статины (n=43) и группа без статинов (n=46). Из 43 пациентов, получавших статины, 31 пациент получал 20 мг аторвастатина в сутки, 12 пациентов - 40 мг аторвастатина в сутки. До включения в исследование ни один из пациентов не получал препараты, модулирующие липидный обмен, включая статины и фибраты. Период наблюдения составил 1 год. Проводился забор крови для исследования биомаркеров. Уровень циркулирующего галектина-3, интерлейкина-6, NT-фрагмента мозгового натрийуретического пептида определяли иммунносорбентным методом.

Гиполипидемический эффект статинов ассоциировался со снижением уровня галектина-3, хотя ответ у пациентов, получавших статины, был неодинаков. Значимых различий в гемодинамических показателях и других биомаркерах не выявлено. Посредством универиантной логистической регрессии выявлено, что галектин-3 (отношение шансов [ОШ] = 1.17; 95% доверительный интервал [ДИ]=1.07–1.29; P=0.002), NT-proBNP (ОШ=1.04; 95% ДИ=1.02–1.10; p<0.05) и терапия статинами (OR=1.07; 95% CI=1.02–1.11; P=0.001) обладают предикторными свойствами кардиоваскулярных событий на протяжении 1 года. После лечения статинами галектин остался независимым предиктором кумулятивных кардиоваскулярных событий (ОШ=1.08; 95% ДИ=1.06–1.11; P=0.001).

Таким образом, результаты проведенного исследования позволяют заключить, что повышенный уровень галектина-3 (>14 нг/мл) является мощным предиктором позитивного эффекта статинов на выживаемость пациентов с регрессей множественной миеломы.

რეზიუმე

გალექტინ-3, როგორც სტატინებით მკურნალობის ეფექტურობის პრედიქტორი პაციენტებში მრავლობითი მიელომით

ბ. სამურა

ზაპოროჟიეს სახელმწიფო სამედიცინო უნივერსიტეტი, უკრაინა

კვლევის მიზანს წარმოადგენდა გალექტინ-3 დონის და სიცოცხლის ხანგრძლივობას შორის ურთიერთკავშირის შესწავლა ავადმყოფებში მრავლობითი მიელომით და კარდიოვასკულარული მოვლენებით.

გამოკვლეულია 89 პაციენტი მრავლობითი მიელომის რეგრესიით. პაციენტები გაყოფილი იყვნენ ორ ჯგუფად: I ჯგუფი შეადგინა 43 ავადმყოფმა, რომელთა მკურნალობაში ჩართული იყო სტატინები; II ჯგუფი - 46 ავადმყოფმა, რომელთა მკურნალობა ტარდებოდა სტატინების გარეშე. 31 პაციენტს I ჯგუფიდან დანიშნული ჰქონდა ატორვასტატინი დოზით 20 მგ დღე-ღამეში, 12 პაციენტს კი - 40 მგ ატორვასტატინი, ასევე დღე-ღამეში. კვლევაში ჩართვამდე არც ერთი მათგანი არ ღებულობდა ლიპიდური ცვლის მოდელირებად პრეპარატებს (სტატინები და ფიბრატები). დაკვირვება მომდინარეობდა 1 წლის განმავლობაში. ხორციელდებოდა ბიომარკერების განსაზღვრა სისხლში; ცირკულირებადი გალექტინ-3,ინტერლეიკინ-6 და ტვინის ნატრიურეტული პეპტიდის NT-ფერმენტის განსაზღვრა ხდებოდა იმუნოფერმენტული მეთოდით.

სტატინების ჰიპოლიპიდური ეფექტი ასოცირებული იყო გალექტინ-3-ის დონის დაქვეითებასთან, თუმცა ამ საკითხზე პაციენტების პასუხი არ იყო ერთგვაროვანი. მნიშვნელოვანი განსხვავება ჰემოდინამიკურ მაჩვენებლებში და სხვა ბიომარკერებში არ გამოვლინდა.
უნივარიანტული ლოგიკური რეგრესიის მეშვეობით ნაჩვენებია, რომ გალექტინ-3 (შანსების დამოკიდებულება [შდ]=1,17; 95%სარწმუნო ინტერვალი [სი]=1.07-1.29; p=0,002), NT-proBNP (შდ=1.04; 95% სი=1.02-1.10; p<0,05) და თერაპია სტატინებით (შდ=1.07; 95% სი=1.02-1.11; p=0,001) ხასიათდებიან კარდიოვასკულარული მოვლენების პრედიქტორული თავისებურებით ერთი წლის მანძილზე. სტატინებით მკურნალობის შემდგომ გალექტინი დარჩა კუმულატური კარდიოვასკულარული მოვლენების დამოუკიდებელ პრედიქტორად (შდ=1,08; 95% სი=1.06-1,11; p=0,001).

პროგნოზულ მოდელში პლაზმური გალექტინის დონის ჩართვის პირობებში სტატინებით მკურნალობამ გამოავლინა პრედიქტორული თვისებები პაციენტებში მრავლობითი მელანომით და გალექტინ-3 <14 ნგ/მლ მაჩვენებლით.