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Clinical and genetic aspects of refractory forms of multiple myeloma development

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Treatment of multiple myeloma has progressed significantly over the past years after the introduction of immunomodulation drugs and proteasome inhibitors. The median of patients survival has improved. All patients with multiple myeloma have relapses during a different time interval. The duration of the achieved remission in patients with a relapse of multiple myeloma becomes shorter with each subsequent case. The choice of regimen for relapse of multiple myeloma is very complex. It depends on a number of factors, including the previous induction regimen, the number of lines of the previous therapy, and the degree of aggression of relapse. The article is devoted to peculiarities of drug resistance formation in the first line therapy in patients with multiple myeloma by assessing of genetic markers (deletion variants of *GSTT1, GSTM1* genes, *GSTP1 (*A313G*), MDR1 (*C3435T*))* and clinical-hematological, laboratory characteristics.

The objective: **to determine the peculiarities of drug resistance establishement in patients with multiple myeloma by assessing of genetic markers (deletion variants of *GSTT1, GSTM1* genes, *GSTP1 (*A313G*), MDR1 (*C3435T*))* and clinical signes (hematological, laboratory characteristics) for predicting the effectiveness of treatment.**

Materials and methods. **We conducted analysis of 68 clinically-laboratory indexes of 130 patients with multiple myeloma and their results of molecular-genetic research of deletion polymorphism of genes *GSTT1, GSTM1,* polymorphism *A313G, C3435T* genes *GSTP1*, *MDR1*.**

***Results*.** **It was determined that important predictors of development of refractory forms of multiple myeloma is allelic polymorphism of gene *GSTM1* of patients, higher level α2-globulin and calcium in blood serum till the beginning of disease.**

Conclusions. **Implementation of predicative model taking into account polymorphism GSTM1, of level α2-globulin and calcium in blood serum till the beginning of treatment raises efficiency of evaluation of individual prognosis of response on treatment.**

Key words*: multiple myeloma, refractory form, gene polymorphism, calcium, alpha-2-globulin.*

Important problem in treatment multiple myeloma (MM) is still choice of optimal First-line treatment. Development of regressions and refractory forms of MM exacerbates prognosis of disease progression and shortens life time of patients [13]. Resistance to drugs is connected with formation of aggressive phenotype of tumor cells of patient, their high polypherative activity and low level of apoptosis [14]. From literary sources it is known that primary medicated resistance can be consequence of inadequate choice of treatment regimens and individual peculiarities of patients, namely, state of their metabolic systems, involved into drugs metabolism [1–3].

From 20 to 40% patients with MM appeared to be indolent to chemotherapeutic treatment (intrinsic resistance) [8], and all patients sensitive to chemotherapy in different periods experience secondary resistance to before conducted therapy [5]. Patients with intrinsic resistance, while chosing other protocol, had shortening of duration of remission after its conduction. Standart protocols used on modern stage in patients with MM provide on the first stage usage of schemes MP, M2, VAD, and their implementation in combination with immunological medications. Above mentioned standard protocols of treatment, according to literary sources, are characterised by high enogh percentage 40-60% of non-effective response on treatment [4, 6, 10], and effective criteria of its prognisis has not been suggested yet.

The objective: search of informative marker for prediction of refractory forms of MM development.

MATERIALS AND METHODS

130 patients with MM from different regions of Ukraine were examined, they were diagnosed for the first time during 2007–2011. Among patients with MM there were 60 (43,79%) male and 77 (56,21%) female. Average age was 56,28±0,96. Diagnosis verifying was conducted in hematologic departments on the basis of clinical presentation analysis, results of radiological, immunochemical (myeloma types G, A, D, Bence Jones), morphologic, histological (needle core biopsy of bone marrow) research, estimation of indicators of hemogramm, biochemical tests, proteinogram of blood serum. Clinical presentation of the majority of patients was with anemic and pain syndromes, associated with proliferation of tumor cells of bone marrow. 30% of investigated had hemorrhagic syndrome developing, 40,4% – intoxication syndrome, 36,5% patients had clinical manifestation against lost of body weight, 67,3% patients had pallor of skin integument. Signs of affect of nervous system in a form of peripheral pain polyneuropathy was determined in 13,5%, hepatomegaly – in 9,6% patients.

Diagnosis verification was conducted according to diagnostic criteria (criteria of determining a diagnosis according B.G. Durie and S.E. Salmon, 1982; classification CRAB, 2003), presence of plasma cells in bone marrow was taken into consideration, as well as level of M-protein in serum of blood/urina, presence of nephatony, anaemia, lytic affect of bones or osteoporosis. Disease state was determined taking into account neoplastic proliferation and correlation between mass of tumor, which was estimated according to paraprotein production by clinical aspects [3]. 46 (35,38%) patients from the total number of investigated had II stage of disease, and 83 (63,84%) – III stage. IIA – in 28 (21,54%) patients, IIБ – in 18 (13,85%), IIIA – in 73 (56,16%) patients; IIIБ – in 10 (7,69%) patients. The total number of patients with absence of nephatony (IA+IIA+IIIA) was 102 (78,46%), and patients with nephatony (IIБ+IIIБ) was 28 (21,53%).

26 (19,11%) of 130 patients with MM undergone treatment according to the scheme MP, 55 (40,44%) – according to the scheme M2, 49 (36,02%) – according to the scheme VAD. Estimation of response on treatment was conducted according to generally accepted criteria EBMT IBMTR ABMTR EGOG (Blade J. et al., 1998), in which the following is identified: com-

Table 1

Clinical characteristic of patients

Indexes (number of patients)	The 1st group, n=52		The 2nd group, n=78	
	n	%	n	%
Women, n=72	30	57,69	42	53,85
Men, n=58	22	42,31	36	46,15
Stage IA, n=1	0	0	1	100
Stage IIA, n=28	12	23,08	16	20,51
Stage IIБ, n=18	8	15,38	10	12,82
Stages IIA+IIБ, n=46	20	38,26	26	33,33
Stage IIIA, n=73	28	53,85	45	57,69
Stage IIIБ, n=10	4	7,69	6	7,69
Stages IIIA+IIIБ, n=83	32	61,54	51	65,38
Stages IIA+IIIA, n=101	40	76,92	61	78,21
Stages IIБ+IIIБ, n=28	12	23,08	16	20,51
Young age (20–34), n=6	2	3,84	4	5,13
Advancing age (35–44), n=14	4	7,69	10	12,82
Middle age (45–59), n=61	27	51,92	34	43,59
Declining years (60 and older i), n=49	19	36,54	30	38,46

Table 2

Laboratory indexes of patients with MM

Laboratory index, unit of measurement	Patients of the 1st group (without response on treatment), n=52	Patients of the 2nd group (with response on treatment), n=78	Results of statistical analysis
Hemoglobulin, g/l	92,25±2,54	96,29±3,32	>0,05
Leucocytes, g/l	5,21±0,18	5,61±0,16	>0,05
Blood platelets, g/l	194,85±19,05	271,2±34,44	>0,05
ESR, mm/hour	43,21±1,42	43,91±1,33	>0,05
Creatinine, mcM/l	103,13±9,50	96,40±6,33	>0,05
Crude protein, g/l	92,53±5,32	95,02±2,05	>0,05
Plasma cells in bone marrow, %	35,32±2,01	32,96±2,18	>0,05
M-gradient, g/l	42,03±2,68	38,23±2,87	>0,05
Albumin, g/l	35,24±1,95	34,03±1,69	>0,05
α2-globulin, g/l	7,25±0,16	6,69±0,18	<0,05
Calcium, mmol/l	2,71±0,03	2,26±0,02	<0,05
Albuminuria, g/l	5,86±3,37	2,55±0,29	>0,05

plete remission, partial remission, minimal response, progressive disease, without response, plateau [4]. Among treated 130 patients: 6 (4,61%) patients had complete remission, 72 (55,38%) – partial remission, 52 (40,00%) – absent response on treatment. 13 (50%) patients, who undergone treatment according to the protocol MP, had effective response, and among those patients, who received M2 response was effective in 33 (60%) patients, among those, who received VAD – in 32 (65%).

For search of informative prognosis markers of response on treatment patients were divided into two groups: the 1st group – 52 patients, who had no response on treatment, the 2nd group – 78 patients with response on treatment, among which there were patients with complete or partial remission. Similar approach was used by researches from France Dumontet C. and at el. (2010), who estimated general response on treatment, summing up in their work complete, very good response and partial response [3]. Investigated patients of both groups undergone detailed analysis of 68 clinically-laboratory indexes and results of molecular-genetic research of deletion polymorphism of genes *GSTT1, GSTM1,* polymorphism *A313G, C3435T* of genes *GSTP1, MDR1.* Molecular-genetic research of deletion polymorphism of genes *GSTT1, GSTM1* was conducted with usage of multicomplex polemerase chain reaction (PChR). Polymorphous variants *A313G, C3435T* of genes *GSTP1, MDR1* were determined with the usage of PChR and method of polymorphism of the length of restriction fragments.

Statistical analysis in groups of comparison for determining informative markers of development of refractoriness were conducted with the usage of the method of binary logistic regression (program SPSS 16.0). For creating accurate statistical model of prognosis of refractory forms MM was implemented method of binary logistic regression with consequent including of predictors (program SPSS 16.0).

RESULTS

Among possible factors of prognosis of response on treatment of patients with MM the following criteria are taken into consideration: age, physical activity, functional status of nephros, dissemination of neoplastic process and intensity of ossifluence processes. It is considered that declining years, renal irritation, pathologic fractures are predictors of unfavorable duration of dis-

Table 3

Rate of deletion polymorphism of genes GSTT1, GSTM1 and polymorphous variants A313G, C3435T of genes GSTP1, MDR1 in comparison groups

Gene	Genotype	The 1st group without response, n=52		The 2nd group with response, n=78		Results of statistical analysis			
		n	%	n	%	χ^2	OR	95%CI	p
GSTT1	*deletion*	13	25,00	12	15,39	1,86	1,83	0,76-4,41	>0,05
	alelle	39	75,00	66	84,61	1,86	0,55	0,23-1,31	>0,05
GSTM1	*deletion*	17	32,70	49	62,82	11,33	0,29	0,14-0,60	<0,001
	alelle	35	67.30	29	37,18	11,33	3,48	1,66-7,29	<0,001
GSTP1 (A313G)	AA	18	34,61	30	38,46	0,02	0,85	0,41-1,76	>0,05
	AG	29	55,77	41	52,56	0,13	1,14	0,56-2,30	>0,05
	GG	5	9,62	7	8,98	0,02	1,08	0,32-3,60	>0,05
MDR1 (C3435T)	CC	14	26,92	20	25,64	0,03	1,07	0,48-2,37	>0,05
	CT	24	46,16	34	43,59	0,08	1,11	0,55-2,25	>0,05
	TT	14	26,92	24	30,77	0,22	0,83	0,38-1,81	>0,05

Table 4

Statistical models of risk development of refractory forms of MM prognosis

Factors, combinations of factors	Model accuracy, %
GSTM1	69,90
Ca/α2-globulin	62,30
GSTM1 /Ca/ α2-globulin	73,60

ease and absence of effective response on treatment. Unfavorable predictors are: A type of myeloma, high level beta2-microglobin, progressive anemia, hypoalbuminemia, thrombocytopenia and activity increase of C-responsive protein, lactic dehydrogenase, α-amylase. Change of laboratory indexes and appearance of pathologic proteins, plasma cells in bone marrow nowadays allow to prognosticate effectiveness of response on treatment [7].

For analysis of 68 clinically-laboratory indexes in investigated by us patients in groups of comparison method of binary logistic regression was implemented. Table 1 shows basic clinical characteristics of patients of the 1st and the 2nd groups.

We conducted comparative analysis of basic characteristics and clinical presentation of disease of patients of both groups. Number of men and women obviously did not differ in comparison groups. Average age of patients in the 1st group was 57±1,54 and obviously did not differ from average age in the 2nd group – 55,79±1,24. In both groups there were patients with different stages and substages of disease, number of patients in subgroups while comparing among them obviously did not differ. We also did not determine obvious differences during comparison number of patients in age subgroups.

Table 2 shows some of the laboratory indexes before beginning of treatment of investigated by us patients, which are used in practical medicine as prognosis markers.

Accurate disparities were determined for indexes of calcium in blood serum. Patients of the 1st group had obviously higher level of calcium as compared with patients of the 2nd group. According to information of some authors, level of calcium in blood serum before beginning of treatment correlates with mass of tumour tissue and intensity of processes of bone ossifluence, that is, by degree of damage of bone tissue [9]. Received results about association of higher level of calcium in blood serum before beginning of treatment with non-effective response coincides with results received by other authors.

Patients of the 1st group also had higher level of α2-globulin as compared with patients of the 2nd group. Raise of level of α2-globulin appeared in chronic infections, allergenic, autoimmune and oncological diseases and correlates with indexes of ESR, C-responsive protein, fibrinogenous and other acute-phase proteins [3]. Investigated by us patients with non-effective response on treatment had raise of α2-globulin, but within normal indicator values (6,0–12,0 g/l), which mediately indicates about functional state of nephros, in particular, higher filtration of protein, loss with urine of albumen, low-molecular globulin, since synthesis of α2-globulin in liver raises in these very conditions. Higher level of α2-globulin in proteionogramma in a form of visual peak (M-gradient or praprotein) is characteristic also for patients with MM [1–4].

Results of molecular-genetic research showed (table 3), that patients of the 1st group had obviously higher rate of deletion polymorphism of gene *GSTM1*, and rate of allelic polymorphism gene *GSTM1* was obviously lowered. While calculating indexes of correlation of chances (OR) we determined, that for circulators of allelic polymorphism of gene *GSTM1* risk of development refractory forms (absence of response on treatment) raises in 3,5.

Differences in rates *GSTT1* of deletion polymorphism and polymorphous variants *A313G*, *C3435T* of genes *GSTP1*, *MDR1* were not determined, that is they did not influence response during conducting specific therapy.

Known data [7, 8] shows that accuracy of effective response on conducted therapy raises on the background of absence of nephatony.

As it was shown above, among treated patients, 28 (21,53%) till the beginning of treatment were diagnosed with nephatony. Since for *GSTM1* allelic polymorphism we showed association with development of refractory forms, forming non-effective response on conducted therapy, we considered it important to analyze influence of this variant of gene on formation nephatony. Among 28 patients with nephatony, allelic polymorphism was determined in 22 (70,96%), and among patients with normal nephros functioning 47 (46,07%), given data obviously differed among each other (χ^2=6,58; p<0,05). In such a way, during presence of allelic polymorphism of gene *GSTM1* of patients, development of MM was accompanied with nephatony more often.

Binary logistic regression with consequent including of 68 clinically-laboratory indexes and results of genetic testing of polymorphism of researched genes in investigated patients was implemented for creating prognostic model (table 4). We clarified that high prognostic value had polymorphism of gene *GSTM1* and indexes of level of calcium and α2-globulin in peripheral blood. The biggest prognostic value for assessment risk

of development refractory forms of MM had statistical model including three mentioned predictors, its accuracy was 73,60%.

So, analysis of polymorphism of gene *GSTM1* of patients with MM for prognosis of treatment effectiveness should be conducted taking into consideration other accurate predictors, since it raises accuracy of statistical model.

After receiving prognostic model with high accuracy we conducted approbation of received results. 10 patients undergone primary genetic testing, before prescription of standard treatment protocol. Four patients who had deletion polymorphism of gene *GSTM1* were prescribed standard therapy and partial remission was required. Indexes of α2-globulin in peripheral blood of these patients were within normal limits, and two patients had higher calcium level (3,05 mmol/l; 3,36 mmol/l). Patients with higher calcium level had worse somatic state at the expense of expressed bone destructions and pathologic fracture; that is why they required corrected accomplishing therapy before beginning of special treatment.

Three of six patients with allelic polymorphism of gene *GSTM1* had progressive disease, in spite of prescribed specific treatment. One of the patients with progression had higher level of α2-globulin, evident clinical indication of nephatony, infectious complications of pulmonary system, thrombembolia of main pulmonary artery, which caused death. Three patients, taking into consideration presence of allelic polymorphism of gene *GSTM1*, were prescribed schemes of therapy with immunological medications. These patients had partial remission. It is important to mention that among six patients with allelic polymorphism calcium level was imperceptibly higher of two patients (2,71 mmol/l; 2,68 mmol/l), one of them had early relapse of disease after treatment according to the scheme MP (without usage of immunological medications).

Thus, while conducting our work, influence of polymorphous variants of gene *GSTM1* on forming phenotype of doctors was shown. Determined discrepancies allow foreseeing that on the background of deletion polymorphism of gene *GSTM1,* with which absence of ferment-isomere is connected, metabolism of cytostatic medications slows, which favors effective response on treatment. While conducting complex analysis it was clarified, that analysis of genetic polymorphism in combination with laboratory indexes raises effectiveness of individual prognosis of refractory forms of MM development.

CONCLUSIONS

1. Allelic polymorphism of gene *GSTM1* of patients is associated with formation of non-effective response on treatment. Risk of development of refractory forms of patients with presence of this polymorphism raises in 3,5.

2. Allelic polymorphism of gene *GSTM1* is associated with development of nephatony of patients with MM.

3. Important predictors of development of refractory forms of MM is raise of the level of α2-globulin and calcium in blood serum of patients till the beginning of treatment.

4. Implementation of predicative model taking into consideration polymorphism *GSTM1,* level of α2-globulin and calcium in blood serum till the beginning of treatment raises effectiveness of individual prognosis of response on treatment.

Клініко-генетичні аспекти розвитку рефрактерних форм множинної мієломи

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Лікування пацієнтів на множинну мієлому значно просунулося вперед протягом останніх років після впровадження імуномоделюючих препаратів і інгібіторів протеосом. Медіана загальної виживаності значно покращилась. Усі пацієнти із множинною мієломою протягом різного періоду часу можуть рецидивувати. Тривалість досягнутої ремісії у пацієнтів із рецидивом множинної мієломи у кожному наступному випадку її досягнення стає менш тривалою. Вибір режиму терапії рецидиву множинної мієломи дуже складний і залежить від чисельних чинників, включаючи попередній режим індукції, кількість ліній попередньої терапії, ступінь агресивності рецидиву. Стаття присвячена визначенню особливостей формування медикаментозної резистентності на першу лінію терапії у пацієнтів із множинною мієломою шляхом оцінювання генетичних маркерів (делеційних варіантів генів *GSTT1, GSTM1*, поліморфізму A313G, C3435T генів *GSTP1, MDR1)* та клініко-гематологічних, лабораторних характеристик.

Мета дослідження: визначення особливостей формування медикаментозної резистентності на першу лінію терапії у пацієнтів із множинною мієломою шляхом оцінювання генетичних маркерів (делеційних варіантів генів *GSTT1, GSTM1*, поліморфізму A313G, C3435T генів *GSTP1, MDR1)* та клініко-гематологічних, лабораторних характеристик для прогнозування ефективності лікування.

Матеріали та методи. Проведено аналіз 68 клініко-лабораторних показників та результатів молекулярно-генетичного дослідження делеційного поліморфізму генів *GSTT1, GSTM1*, поліморфізму A313G, C3435T генів *GSTP1, MDR1* у 130 хворих на множинну мієлому.

Результати. Виявлено, що важливими предикторами розвитку рефрактерних форм множинної мієломи є алельний поліморфізм гена *GSTM1* у хворих, підвищений рівень альфа-2-глобуліну та кальцію у сироватці крові до початку лікування.

Заключення. Застосування прогностичної моделі з урахуванням поліморфізму гена *GSTM1*, рівня альфа-2-глобуліну та кальцію у сироватці крові до початку лікування підвищує ефективність оцінювання індивідуального прогнозу відповіді на лікування.

Ключові слова*: множинна мієлома, рефрактерні форми, поліморфізм генів, кальцій, альфа-2-глобулін.*

Клинико-генетические аспекты развития рефрактерных форм множественной миеломы

Н.И. Костюкова, З.И. Россоха, Н.Г. Горовенко, С.В. Выдыборец

Лечение пациентов с множественной миеломой значительно продвинулось в течение последних лет после внедрения иммуномодулирующих препаратов и ингибиторов протеосом. Медиана выживаемости значительно улучшилась. Все пациенты с множественной миеломой в течение разного временного периода могут рецидивировать. Длительность достигнутой ремиссии у пациентов с рецидивом множественной миеломы в каждом следующем случае ее достижения становится короче. Выбор режима терапии рецидива множественной миеломы очень сложный и зависит от множества факторов, включая предыдущий режим индукции, количество линий предшествующей терапии, степень агрессивности рецидива. Статья посвящена определению особенностей формирования медикаментозной резистентности на первую линию терапии у пациентов с множественной миеломой путем оценки генетических маркеров (делеционных вариантов генов *GSTT1, GSTM1*, полиморфизма A313G, C3435T генов *GSTP1, MDR1)* и клинико-гематологических, лабораторных характеристик.

Цель исследования: определение особенностей формирования медикаментозной резистентности на первую линию химиотерапии у пациентов с множественной миеломой путем оценки генетических маркеров (делеционных вариантов генов *GSTT1, GSTM1*, полиморфизма A313G, C3435T генов *GSTP1, MDR1)* и клинико-гематологических, лабораторных характеристик для прогнозирования эффективности лечения.

Материалы и методы. Проведен анализ 68 клинико-лабораторных показателей и результатов молекулярно-генетического исследования делеционного полиморфизма генов *GSTT1, GSTM1*, полиморфизма A313G, C3435T генов *GSTP1, MDR1* у 130 больных множественной миеломой.

Результаты. Обнаружено, что важными предикторами развития рефрактерных форм множественной миеломы является аллельный полиморфизм гена *GSTM1* у больных, повышенный уровень альфа-2-глобулина и кальция в сыворотке крови до начала лечения.

Заключение. Применение прогностической модели с учетом полиморфизма гена *GSTM1*, уровня альфа-2-глобулина и кальция в сыворотке крови до начала лечения повышает эффективность оценки индивидуального прогноза ответа на лечение.

Ключевые слова: *множественная миелома, рефрактерные формы, полиморфизм генов, кальций, альфа-2-глобулин.*

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