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ORIGINAL ARTICLE

Free light chains ratio as a marker to estimate prognosis and survival in patients with multiple myeloma and primary amyloidosis

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Summary

Purpose: *The aim of this study was to evaluate the significance of free light chains ratio (FLC ratio) as a prognostic factor for remission, progression and survival in patients with multiple myeloma (MM) and primary amyloidosis.*

Methods: *The concentrations of immunoglobulins and FLC ratio were measured using immunonephelometry. A total of 101 patients from 3 different disease groups were investigated during a 7-year period: 1) MM (n=95); 2) nonsecretory multiple myeloma (NSMM) (n=3); and 3) primary amyloidosis (n=3). Reference range for FLC ratio was 0.26-1.65.*

Results: *According to the International Staging System (ISS) for MM, abnormal serum FLC ratio was < 0.03 or > 32. Patients with MM and highly or intermediately abnormal FLC ratio and a combination of adverse risk factors (56.9%) had median survival of 26 months (range 16-38), as opposed to patients with normal or slightly changed values of FLC ratio without adverse risk factors (43.1%) with median survival of 45 months (range 27-69). Also, all of the patients with NSMM had slightly changed values of FLC ratio corresponding to low risk of disease progression. In patients with primary amyloidosis, 33.3% had slightly changed values of FLC ratio corresponding to low risk of disease progression, as opposed to 66.7% with abnormal FLC ratio, corresponding to high risk.*

Conclusion: *Abnormal FLC ratio in the examined groups could be an independent risk factor of disease progression and worse prognosis.*

Key words: free light chains ratio, multiple myeloma, nonsecretory multiple myeloma, primary amyloidosis, prognostic factors

Introduction

Plasma cells synthesize the immunoglobulins (Ig), which consist of 2 heavy chains (HC) and 2 kappa (κ) or lambda (λ) polypeptide light chains (LC). Under normal conditions, the concentration of polyclonal free κ and λ FLC are 3-19 and 5-26 mg/L, respectively. In abnormal conditions, one or several clones of B lymphocytes or plasma cells synthesize only LC of Ig, of κ or λ type in excessive amounts [1]. MM is a malignant disease, characterized by abnormal local (solitary myeloma) or diffuse (MM) proliferation of abnormal plasma cells in the bone marrow, that rarely move into peripheral blood (plasma cell leukemia). Abnormal plasma cells synthetize and shed increased quantities of certain types of Ig (IgA, IgG, IgD, IgE) or LC (κ and λ) into blood, and cause characteristic osteolytic bone lesions. MM is the second commonest haematological malignancy, just after non-Hodgkin lymphoma; generally, it is the disease of elderly people and it rarely appears (approximately 2%) in patients younger than 40 years. There is a mild tendency towards males [2]. Median survival time is approximately 33 months [3]. The cause of MM is still unknown [4]. The strongest factor related with the risk of MM development is the presence of monoclonal gammopathy of undetermined significance (MGUS) [5]. MM is the prototype of monoclonal dyscrasia of plasma cells. It is divided into two subclasses: indolent form of latent MM and symptomatic systemic disease that often includes grave lesions of kidney, bones or bone marrow.

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Indolent disease is characterized by lack of symptoms, without or with a few bone lesions and a stable concentration of monoclonal (M) Ig protein [6]. About 3-4% of patients with MM belong to the group of NSMM [2]. Primary amyloidosis belongs to a group of monoclonal plasma cell disorders, whose main characteristic is extracellular disposal of Ig LC fibril into various tissues, resulting in dysfunction of multiple organs [7]. A sensitive latex agglutination test is used for the detection of Ig LC, which differs from earlier LC tests in that new polyclonal antibodies react only with epitopes that are hidden when connected with HC, but available when not connected with HC [8]. Testing for FLC enables quantitative monitoring of patients with oligosecretory plasma cells disorders, including primary amyloidosis, oligosecretory MM and approximately 2/3 of the patients with NSMM [9]. The concentration of serum FLCs is more sensitive, accurate and precise indicator for detection, characterization and monitoring of the course of various types of paraproteinemia. Urinalysis is not a reliable evidence of the change of concentration of synthetized FLCs [10]. Reduction of FLC ratio by more than 50% in relation to value of the beginning of therapy, in parallel with the maintaining of unchanged values of intact monoclonal Ig, is the first indicator of good response to the therapy [8].

Methods

In this prospective clinical study that lasted from 2004 to 2010, the patients (n=101) were divided into 3 groups:

1. A group including patients with MM (n=95).
2. A group including patients with NSMM (n=3).
3. A group including patients with primary amyloidosis (n=3).

Thorough clinical examination were done for all 3 groups, and based on them, the patients were classified in suspected clinical diagnoses. Serum samples (2 ml) for protein measurement were taken in the morning in vacutainers without anticoagulant from inpatients and outpatients. After blood collection and spontaneous coagulation at room temperature samples were centrifuged at 5000 rpm. and analyses were done in fresh sera immediately; some samples were kept at –20° C up to one month, and for longer periods, they were stored at –70° C. Quantitative determination of FLC and classes (isotypes) of Ig was done by automated immunonephelometric method on SIEMENS DADE Behring II analyzer with reagents (FREELITE, The Binding Site, UK), according to the instructions of the manufacturer in software programs for each analytical parameter.

Statistical considerations

The results were registered as individual or mean values with standard deviation (SD). Sensitivity (SN), specificity (SP), positive predictive value (PPV) and negative predictive value (NPV) were used to determine the value of diagnostic test (FLC cut-off value 300 mg/L) on the probability of appearance of low and high risk of disease progression. The low risk category was obtained with a risk index 0 and 1 and the high risk category with a risk index 2 and 3. For testing the differences between groups, the Mann-Whitney U test was performed. Chi-square (x^2) test was used for categorical frequency data between groups. A p-value of less than 0.05 was considered significant. The obtained data were processed through the Stat for Windows, R.4.5. software package.

Results

At the time of diagnosis of 89/95 (93.7%) patients in the MM group had concentrations of FLCs deviating from the reference interval (κ=3.3-19.4; λ=5.71-26.3) mg/L. Concentrations of FLCs of κ-type ranged from 4.5 to 2220.0 mg/L, and for FLCs of λ-type from 4.0 to 796.0 mg/L. Figure 1 illustrates the values of FLC ratios and the relative risk (RR) in all patients of this group. The results obtained with immunonephelometry showed that 12 (12.6%) patients had FLC ratios within the reference interval (0.26-1.65) and median survival of 51 months (range 33-69), and 25 (26.4%) had highly abnormal FLC ratios (< 0.03 or > 32) and median survival of 22 months (range 16-28). The remaining 29 (30.5%) patients had intermediately abnormal FLC ratios (< 0.125 or > 8) (median survival 30 months, range 22-38), and 29 (30.5%) had low abnormal FLC ratios (< 0.26 or > 1.65) with median survival 39 months (range 27-51) (Table 1). Based on the value of FLC ratio, more than half of the patients had intermediate and highly abnormal FLC ratios, and thus they were at higher intermediate and high relative risk (RR) of disease progression and poorer prognosis (Figure 1).

In the group of patients with NSMM, at the time they were diagnosed, 3/3 (100%) patients had concentrations of FLCs deviating from the reference interval. The determined concentrations of FLCs of κ-type ranged from 0.27 to 165.99 mg/L, and of λ-type from 8.2 to 86.5 mg/L. The results obtained with the immunonephelometry showed that 3/3 (100%) patients had low abnormal FLC ratios (< 0.26 or > 1.65), and thus

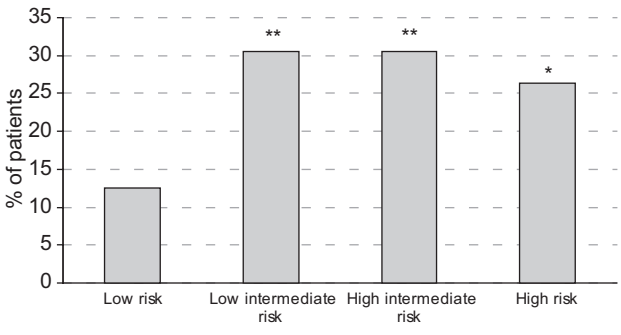

Figure 1. κ/λ FLC and relative risk in 95 patients with multiple myeloma. *x^2 = 4.83, p <0.05, **x^2 = 7.96, p <0.01, vs. low risk patients.

Table 1. Risk factors and survival in 95 patients with multiple myeloma according to ISS

Class (isotype) of Ig (n=number of patients)	*FLC ratio*	*Sβ2M (g/L)*	*Serum albumin (g/L)*	*ISS - median survival (months)*	*Relative risk of disease progression*
IgGκ (n=6) IgA λ (n=4) IgM λ (n=1) BG λ (n=1)	0.26-1.65 12/95 (12.6%)	<3.5	≥35	(0 risk factors ~ 51 months)	Low risk
IgGκ (n=19) IgAκ (n=5) IgM λ (n=3) BGκ (n=1) TG λ (n=1)	< 0.26 or > 1.65 29/95 (30.5%)	<3.5	≥35	(1 risk factors ~ 39 months)	Low intermediate risk
IgGκ (n=12) IgMκ (n=10) IgAκ (n=3) IgEκ (n=1) BGκ (n=3)	< 0.125 or > 8 29/95 (30.5%)	≥3.5-5	≥35	(2 risk factors ~ 30 months)	High intermediate risk
IgGκ (n=7) IgMκ (n=7) IgA λ (n=7) BGκ (n=1) TG λ (n=2) QG λ (n=1)	< 0.03 or > 32 25/95 (26.4%)	≥5	<35	(3 risk factors ~ 22 months)	High risk

ISS: international staging system, BG: biclonal gammopathy, TG: triclonal gammopathy, QG: quadriclonal gammopathy, Ig: immunoglobulin; FLC: free light chain, FLC ratio: κ/λ ratio, Sβ2M: serum β_2-microglobulin

lower RR of disease progression and rather good prognosis (Table 2). Also, in the group of patients with primary amyloidosis, at the time they were diagnosed, 3/3 (100%) patients had concentrations of FLCs deviating from the reference interval. Determination of concentration of FLCs of κ-type ranged from 8.0 to 1490.0 mg/L, and of λ-type from 5.8 to 1988.0 mg/L. The results obtained with immunonephelometric method showed that 2/3 (66.7%) patients had highly abnormal FLC ratios (< 0.03 or > 32), with the presence of other risk factors (sedimentation of amyloids, high serum β_2-microglobulin and low serum albumin). These patients had high RR of disease progression, and thus a poor prognosis. In 1/3 (33.3%) patient, the values of FLC ratios slightly deviated from the reference interval (< 0.26 or > 1.65). This patient had low RR of disease progression, and thus better prognosis (Table 3).

There was no significant difference between the 2 groups (kappa or lambda ≤ 300 mg/L; kappa or lambda > 300 mg/L) regarding blood β_2-microglobulin concentration (Tables 4 and 5).

Discussion

In our study 93.7% of the patients with MM had abnormal concentrations of FLCs, of κ-type and/or λ-type, as a result of renal damage or bone marrow suppression. The purpose of checking these values was to make a diagnosis as early as possible, as with any ma-

Table 2. Risk factors and survival in 3 patients with non secretory multiple myeloma according to ISS

Type of LC Ig (n=number of patients)	*FLC ratio*	*Sβ2M (g/L)*	*Serum albumin (g/L)*	*ISS - median survival (months)*	*Relative risk of disease progression*
κ (n=0) λ (n=0)	0.26-1.65 0 (0%)	<3.5	≥35	(0 risk factors ~ 51 months)	Low risk
κ (n=1) λ (n=2)	<0.26 or >1.65 3/3 (100.0%)	<3.5	≥35	(1 risk factors ~ 39 months)	Low intermediate risk
κ (n=0) λ (n=0)	<0.125 or >8 0 (0%)	≥3.5-5	≥35	(2 risk factors ~ 30 months)	High intermediate risk
κ (n=0) λ (n=0)	<0.03 or >32 0 (0%)	≥5	<35	(3 risk factors ~ 22 months)	High risk

ISS: international staging system, LC: light chain, Ig: immunoglobulin, FLC: free light chain, FLC ratio: κ/λ ratio, Sβ2M: serum β_2-microglobulin

Table 3. Risk factors in 3 patients with primary amyloidosis

Type of LC Ig (n=number of patients)	*FLC ratio*	*Sβ2M (g/L)*	*Serum albumin (g/L)*	*Relative risk of disease progression*
λ (n=1)	< 0.26 or >1.65 1 (33.3%)	< 3.5	≥ 35	Low risk
κ (n=1) λ (n=1)	< 0.03 or > 32 2 (66.7%)	≥ 5	< 35	High risk

For abbreviations see footnote of Table 2

Table 4. Serum free light chains characteristics at cut-off value in newly diagnosed multiple myeloma patients

Parameters	*Test*	*Risk assessment*		*SN (%)*	*SP (%)*	*PPV (%)*	*NPV (%)*
		High	*Low*				
kappa or lambda (mg/L)	> 300	(TP) 15	(FP) 12	28.0	70.0	55.0	43.0
	≤ 300	(FN) 39	(TN) 29				
Total (n)		54	41				

TP: true-positive, FP: false-positive, FN: false-negative, TN: true-negative, SN: sensitivity, SP: specificity, PPV: positive predictive value, NPV: negative predictive value, Low risk: risk index 0 and 1, High risk: risk index 2 and 3

Table 5. Serum β_2-microglobulin values at cut-off value of serum free light chains in newly diagnosed multiple myeloma patients

kappa or lambda (mg/L)	*β_2-microglobulin (g/L)*	
	X	*SD*
≤ 300	5.98	6.79
> 300	6.18	5.93
Mann-Whitney U test	Z = 0.89	p = 0.3733

lignant disease. It was very important to establish the importance of FLC ratio, as a prognostic factor for remission, progression and survival in the patient groups. According to ISS, the values of FLC ratio at initial diagnosis were taken as an important indicator of MM prognosis. Specifically, abnormal FLC ratio (< 0.03 or > 32), high serum β_2-microglobulin (≥ 3.5 g/L) or low serum albumin (< 35 g/L), were defined as adverse risk factors. According to the above mentioned criteria, patients with any combination of 0, 1, 2 or 3 adverse risk factors had significantly different FLC ratios in overall survival, with median survival time of 51, 39, 30 and 22 months, respectively (p<0.001) [11]. Median survival of patients with 3 risk factors was less compared with patients with 0 factors [median: 51 months with 0 factors, 39 months with 1 factor (p=0.13), 30 months with 2 factors (p=0.001) and 22 months with 3 factors (p<0.001)] [11]. According to Bradwell et al. [12] the values of FCL ratio are not significant indicators of the change of the disease course in relation to the basic Ig molecule isotype in the group with MM, so their repeated laboratory determination is not indicated. It was noticed that sometimes the patients with MM can abruptly develop heavy and irreversible renal damage indicating that high concentrations of FLCs are toxic to the kidneys. The amount of serum FLCs necessary to cause renal impairment was studied by Nowrousian et al. [13]. As renal impairment develops, progressive increase occurs in both the monoclonal serum FLCs and the polyclonal non-tumor serum FLCs. Concentrations of monoclonal serum FLCs below 300 mg/l are rarely associated with renal impairment as judged by the associated normal levels of the non-tumor FLCs. These concentrations are somewhat higher than those observed by Nowrousian et al. [13] in patients with renal impairment, but are in the same general ran ge. It is important to mention that renal failure (RF) is the main cause of morbidity and mortality of patients with MM. According to the previously mentioned ISS criteria [11], our results showed that 56.9% OF patients with high or intermediate abnormal FLC ratio and a combination of adverse risk factors had median survival time of approximately 22-30 months, as opposed to 43.1% patients with normal or slightly changed FLC ratio, without adverse risk factors, with median survival of about 39-51 months (Table 1). Similar to what other authors determined [11], 25 (26.4%) patients had highly abnormal values of FLC ratio (< 0.03 or > 32), shorter median survival and poorer prognosis. These patients suffered from an aggressive type of MM that demands a more aggressive chemotherapeutic approach, by applying high-dose chemotherapy and autologous stem-cell transplantation (SCT). During our study, 4 (4.2%) patients died during or after thera-

py. They had poor response to therapy, highly abnormal values of FLC ratio (< 0.03 or > 32) and median survival time of about 22 months.

MM can exist for years without visible signs of disease. As a rule, the symptoms appear only after the disease has existed for many years [12]. Therapy makes sense only if preceded by a precise diagnosis. In this context, it is important to consider the patients with asymptomatic ("smoldering") MM that satisfy two basic criteria for active (symptomatic) MM: Monoclonal (M) protein in serum > 30 g/L, and/or clonal plasma cells in bone marrow ≥ 10%, but without symptoms or damages of organs or tissues connected with myeloma, including bone lesions. In these patients, the disease usually appears after 2-4 years [14], and that is why they should be monitored regularly. Unlike the patients with MGUS, where the risk of progression remains constant over time, in asymptomatic patients with MM the risk is highest within the first several years. According to ISS criteria [11], FLC ratio < 0.125 or > 8 was taken as cut off value. Our results showed that 29 (30.5%) patients had intermediate abnormal values of FLC ratio (< 0.125 or > 8) (Table 1). These patients showed 2.3-fold higher risk of progression into MM, in relation to the patients with FLC ratio of 0.125-8. In a Mayo Clinic study, Snozek et al. showed that abnormal concentrations of FLCs indicate increased risk of progression into MM [11]. Viewed from the clinical and laboratory aspect, we found that it is extremely important to constantly and carefully monitor these patients to discover the transition to symptomatic disease early. In our study, at the time they were diagnosed, 3/3 (100%) patients with NSMM had abnormal concentrations of FLCs of κ and/or λ-type. It is important to emphasize that patients with FLCs concentrations > 150 mg/L are at high relative risk of disease progression and they have poorer prognosis. According to ISS criteria [11], the results we obtained showed that all NSMM patients had slightly changed values of FLC ratio (< 0.26 or >1.65), without adverse risk factors (Table 2). This practically means that these patients were at lower-intermediate RR of disease progression, and thus they had good prognosis. Patients with NSMM were younger and successfully went through autologous SCT. In our study, we also determined the concentrations of FLCs in the group of patients with primary amyloidosis. During the period from 2004 to 2010 there were not many patients in our "bank of serum". This should not be surprising, because it is a disease with a frequency of only 1-5% within monoclonal gammopathies (MG) [15]. According to the literature, at the time the patients were diagnosed, concentrations of FLCs were abnormal in 95% of the patients. Plasma cells clone synthesizes monoclonal FLC, more often of λ-type (1 κ-type: 2 λ-type) [15]. Patients with FLCs concentrations > 150 mg/L are at high RR of disease progression and have poorer prognosis. In most of the patients, FLCs concentrations range between 30.0-500.0 mg/L [15]. In our study, at the time the patients were diagnosed, 3/3 (100%) patients with primary amyloidosis had abnormal concentrations of FLCs, of κ and/or λ-type. In 2 patients, plasma cells clones synthesized monoclonal FLC of λ-type (Table 3). Other authors obtained similar results as well [15]. During the present study, 2/3 (66.7%) patients with primary amyloidosis whose concentrations of FLCs were > 1450.0 mg/L, died during or after the applied therapy. They had low response to therapy, highly abnormal values of FLC ratio (< 0.03 or > 32), high RR of disease progression and thus poorer prognosis. We observed that amyloids were deposited in the heart and the digestive tract of these patients. These abnormal proteins are usually infiltrating the heart (around 50% of the cases), kidneys, liver and gastrointestinal tract [15]. Having in mind everything said so far, we found that FLCs were directly cardiotoxic and that the treatment did not provide satisfactory results. In 1/3 (33.3%) patient with primary amyloidosis FLC ratio was slightly deviated from the reference interval (< 0.26 or >1.65). This patient was at low RR of disease progression (Figure 3) and thus had good prognosis (Table 3). According to the relevant literature, the mean survival time of these patients is slightly longer than 18 months [7]. Owing to current laboratory techniques (serum FLC measurement) and the newer generation of cytotoxic drugs, the median survival is 6-8 years [15]. These results are very close to our findings. Viewed from the clinical and laboratory viewpoint, by applying adequate therapy that largely extends the duration of disease remission, as well as by routine, repeated determination of FLC, disease prognosis would be improved. It is considered that the diagnosis of primary amyloidosis is far more common and that in many cases it is wrongly diagnosed as smoldering MM, which points out to the importance of early and precise diagnosis and timely beginning of appropriate treatment. Until the 1990s, tests for measuring serum monoclonal Ig included electrophoresis (EF), immunoelectrophoresis (IEF), immunofixation electrophoresis (IFE) and nephelometric determination of serum Ig heavy chains. For most of the patients with MGUS and MM, these diagnostic tests proved to be sufficient. Nevertheless, for most of the patients with primary amyloidosis and for more than 3% of the patients with nonsecretory or oligosecretory myeloma, these tests proved to be insufficient [17]. During our research and monitoring, the patients were submitted to some of the therapeutic protocols for MM: MP protocol (melphalan/prednisone) or

MPT protocol (melphalan/prednisone/thalidomide) for patients older than 65 years or younger than 65 years respectively, but were not candidates for autologous SCT. VAD protocol (vincristine/adriamycin/dexamethasone) and CTD protocol (cyclophosphamide/thalidomide/dexamethasone) were administered to patients younger than 65 years, who were candidates for autologous SCT. Interferon and thalidomide were used as maintenance therapy after autologous SCT in the last 4 years (2007-2010). From the first group (MM), approximately 34% of the patients who –during therapy– showed decrease of FLC ratio > 50% achieved disease remission. The time to achieve remission and the length of its duration determined the overall survival time [18]. By quantification of the concentrations of FLCs we obtained much more realistic results for patients with MM, NSMM and primary amyloidosis [18].

The cut-off value for κ and λ chains (≤300 to >300 mg/L) in newly diagnosed MM patients is of minimal utility for the precise evaluation of high-risk population due to its low sensitivity and specificity.

The proposed cut-off concentration of FLC and β_2-microglobulin, as well as individual risk factors can not sufficiently help the clinician foresee the evolution of the disease.

Conclusion

The existence of a significantly abnormal FLC ratio in the examined groups represents an independent risk factor for disease progression and poorer prognosis. The reduction of FLC ratio and monoclonal Ig to normal values, under the influence of the applied therapy indicates good response and adequate choice of therapy. Based on all the presented results, we can generally conclude that quantification of FLCs (FLC ratio) is necessary and represents a new diagnosis of paraproteinemias.

References

1. Mijuskovic Z, Radovic V, Pejovic J, Tukic Lj, Marjanovic S, Stojanovic J. Free light chains of immunoglobulin as a prognostic factor of some plasmaproliferative diseases. J Med Biochem 2011; 30: 1-5.
2. International Myeloma Working Group. Criteria for the classification of monoclonal gammopathies, multiple myeloma and related disorders: a report of the International Myeloma Working Group. Br J Haematol 2003; 121: 749-757.
3. Kyle RA, Gertz MA, Witzig TE et al. Review of 1027 patients with newly diagnosed multiple myeloma. Mayo Clin Proc 2003; 78: 21-33.
4. Herrinton LJ, Weiss NS, Olshan AF. Epidemiology of myeloma. In: Malpas JS, Bergsagel DE, Kyle R, Anderson K (Eds): Myeloma: biology and management. Oxford: Oxford University Press, 1998, pp 150-186.
5. Vescio RA, Cao J, Hong CH et al. Myeloma Ig heavy chain V region sequences reveal prior antigenic selection and marked somatic mutation but no intraclonal diversity. J Immunol 1995; 155: 2487-2497.
6. Traynor AE, Noga SJ. NCCN: Multiple myeloma. Cancer Control 2001; 8: 78-87.
7. Premuzic-Lampic M. Hematology, Clinical and Laboratory. Medical Publishing, Zagreb, 2000, pp 175-176.
8. Dispenzieri A, Kyle R, Merlini G et al. International Myeloma Working Group guidelines for serum free light chain analysis in multiple myeloma and related disorders. Leukemia 2009; 23: 215-224.
9. Radovic VV. Recommendations for use of free light chain assay in monoclonal gammopathies. J Med Biochem 2010; 29: 1-8.
10. Waller KV, Ward KM, Mahan JD, Wismatt DK. Current concepts of proteinuria. Clin Chem 1989; 35: 755-765.
11. Snozek CL, Katzmann JA, Kyle RA et al. Prognostic value of the serum free light chain ratio in patients with newly diagnosed myeloma and proposed incorporation into the International Staging System. Leukemia 2008; 22: 1933-1937.
12. Bradwell AR, Carr-Smith HD, Mead GP, Harvey TC, Drayson MT. Serum test for assessment of patients with Bence Jones myeloma. Lancet 2003; 361: 489-491.
13. Nowrousian MR, Brandhorst D, Sammet C et al. Serum free light chain analysis and urine immunofixation electrophoresis in patients with multiple myeloma. Clin Cancer Res 2005; 11: 8706-8714.
14. Kyle RA, Remstein ED, Therneau TM et al. Clinical course and prognosis of smoldering (asymptomatic) multiple myeloma. N Engl J Med 2007; 356: 2582-2590.
15. Dispenzieri A, Lacy MQ, Katzmann JA et al. Absolute values of immunoglobulin free light chains are prognostic in patients with primary systemic amyloidosis undergoing peripheral blood stem cell transplantation. Blood 2006; 107: 3378-3383.
16. Gertz MA, Lacy MQ, Dispenzieri A, Hayman SR. Amyloidosis: diagnosis and management. Clin Lymphoma Myeloma 2005; 6: 208-219.
17. Radović VV. Monoclonal gammopathy of undetermined significance and monoclonal free light chains of immunoglobulins. Arch Pharm 2010; 3: 285-296.
18. Child JA, Morgan GJ, Davies FE et al. High-dose chemotherapy with hematopoietic stem-cell rescue for multiple myeloma. N Engl J Med 2003; 348: 1875-1883.