International prognostic index (IPI) – a critical comparison with five multiple myeloma staging systems in the group of 270 patients treated by conventional chemotherapy*

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In the group of 270 patients with multiple myeloma (MM) treated during 1991–2004 by conventional chemotherapy, the prognostic value and practical utility of IPI (International Prognostic Index) was assessed and compared with five other actual staging systems. Prognostic significance was assessed using the curves of overall survival (OS) according to Kaplan-Meier and log rank test ($p<0.05$). Good practical utility and prognostic significance of Durie-Salmon (D-S) system was confirmed ($p<0.001$). Good overall prognostic significance was observed in simple staging systems based on the measurement of β_2-microglobulin and albumin serum levels according to Bataille ($p<0.001$), SWOG (South West Oncology Group, $p<0.001$) and IPI ($p<0.001$). Regardless of a short 5-year duration of the study, the scoring system according to San Miguel enclosing apart from other parameters also propidium iodide proliferation index (PC-PI) of myeloma plasmocytes seems to be promising with very different characteristics of curves of overall survival ($p<0.001$). Very good prognostic value and easy practical utility were examined in Olomouc staging system (OSS) based on the measurement of β_2-microglobulin and thymidinekinase serum levels ($p<0.001$). With regard to detection of patients of stage 1, i. e. "low risk", not requiring an immediate initiation of conventional chemotherapy ("wait and see" approach), the most suitable was the system according to D-S, SWOG and IPI (median OS 77, 76 and 77 months). To select a cohort of "high risk" patients, i.e. stage 3, with very unfavourable disease prognosis, the most advantageous was the system OSS and San Miguel (median OS was 5 and 6 months) and/or SWOG system selecting patients of stage 4, i.e. "worst prognosis", with median OS 8 months. It was found that IPI did not meet expectations for effective identification of "high risk" patients (median OS of stage 3 was 20 months) nor for the distinction of different prognosis of patients during initial 25 months of MM course at stage 2 vs. 3.

The study indicates that under conditions of common clinical practice and conventional chemotherapy, the staging system according to D-S is still useful, while practical application of SWOG and IPI as simpler alternative to the assessment of clinical stage should be verified by further comparative studies. In harmony with the progress in cytogenetics and molecular biology as well as a prospective requirement of individual target therapy, a future suitable stratification system should be based on parameters of internal biological properties of myeloma tissue and microenvironment of bone marrow, allowing in addition a continuous evaluation of the disease course and the effect of therapy.

Key words: multiple myeloma, clinical staging systems, International Prognostic Index, new independent prognostic factors

A striking clinical and prognostic heterogeneity of multiple myeloma with overall survival varying from several months to over 10 years requires such staging system, that would allow stratification of patients into clearly defined and significantly different prognostic groups with respect to the optimal and individually chosen therapy [1]. Since the pioneer study of Carbone in 1967 [2], over 40 stratification systems have been introduced that are based on newly recog-

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nized prognostic factors expressing in detail the properties of myeloma tissue and microenvironment of bone marrow as well as the macroenvironment of the organism [3]. The first staging systems comprised mostly parameters of tumour size and the range of renal impairment (2, 4–10); recent staging criteria cover mostly the internal biological properties of myeloma plasma cells and microenvironment of bone marrow. Due to good progress in recognition of MM nature and subsequently introduced new methods of intensive therapy, the classical and commonly used staging system according to Durie-Salmon showed to be less efficient [11] and with regard to a high-dose (HD) therapy with autologous stem cell transplantation (ASCT) lost to a great extent its prognostic importance [12]. Out of numerous new stratification systems based mainly on the evaluation of serum level of β_2-microglobulin, the recommended system at present is especially the IPI (International Prognostic Index) developed by IMWG (International Myeloma Working Group) for patients treated by conventional and HD-therapy with ASCT support [13, 14].

The aim of the present study is to compare the prognostic reliability and practical application of IPI [13, 14] with 4 novel stratification systems in MM [15–19) as well as with standard clinical staging system according to Durie-Salmon in the group of patients treated by conventional chemotherapy.

Patients and methods

The analyzed group of 270 symptomatic multiple myeloma patients diagnosed according to the criteria of the South West Oncology Group (SWOG) was examined before initiation of therapy during 1991–2004 [7, 20–22]. The median age of the cohort study was 63 years (range 28–91), with M/F ratio 0.9/1.0; 65% cases of IgG, 22% IgA, 10% Bence-Jones production only, 2% nonsecretory, 0.5% IgD and 0.5% biclonal type, the serum monoclonal light chain was kappa in 58% and lambda in 42%. A systematic conventional chemotherapy, i.e. VBMCP (M_2 protocol), VAD, CyVAD, CIDex, and sometimes MP regimens were used. Overall survival (OS) was considered from the time of MM diagnosis to the death. The median OS for the whole series after elimination of the patients fulfilling criteria of the HD-therapy with ASCT was 32 months. In each patient, the most relevant clinical and laboratory disease characteristics at diagnosis were evaluated. Serum β_2-microglobulin ($ß_2M$) levels were measured by a radioimmunoassay method (RIA kit, ADICO Prague, normal range 0.9–2.4 mg/l), thymidine kinase (TK) serum levels by a radioenzymoassay (REA kit, ADICO Prague, normal range 0–10 U/l). Plasma cell proliferation activity (proportion of S-phase plasma cells) was measured by means of propidium iodide index (PC-PI) by flow cytometry using a DNA/CD_{138} double staining technique. PC-PI was examined in a bone marrow aspirate, after separation of analyzed cells using a density gradient (multiparametric analysis of 2000–4000 cells), special software (Multicycle for Windows ver. 3.0 Phoenix Flow Systems) was used [18, 23]. The patients' data were analyzed according to the criteria of the 6 staging systems. Overall survival curves for each staging system were calculated by the method of Kaplan-Meier and compared using the log rank test ($p<0.05$).

1. IPI i.e. International Prognostic Index by IMWG (13, 14): stage 1 – $\beta_2M<3.5$ mg/l, albumin ≥35 g/l; stage 2 – $\beta_2M<3.5$, albumin <35 or β_2M 3.5–5.5; stage 3 - $\beta_2M>5.5$.

2. DURIE and SALMON [7, 20]: stage I – all of: Hb>100 g/l, S-Ca≤2.9 mmol/l, normal X-ray or 1 bone lesion only, low M-component – IgG<50 g/l, IgA<30 g/l, Bence-Jones proteinuria <4 g/day; stage II – neither stage I nor stage III; stage III – one or more of: Hb<85 g/l, S-Ca>2.9 mmol/l, advanced (>3) lytic bone lesions, high M-component i.e. IgG>70 g/l, IgA>50 g/l, B-J proteinuria >12 g/day. Subclassification: A – serum creatinine value <177 μmol/l, B -- serum creatinine value ≥177 μmol/l.

3. BATAILLE et al [15, 16]: stage 1 ("low risk") – serum $\beta_2M<6$ mg/l, albumin >30 g/l; stage 2 ("intermediate") – β_2M ≥6 mg/l, albumin >30 g/l; stage 3 ("poor risk") – albumin ≤30 g/l.

4. SWOG staging system (South West Oncology Group) [20, 17]: stage 1 ("best prognosis") – β_2M <2.5 mg/l; stage 2 ("good prognosis") – β_2M ≥2.5–<5.5 mg/l; stage 3 ("poor prognosis") – β_2M ≥5.5 mg/l, albumin ≥30 g/l; stage 4 ("worst prognosis") – β_2M ≥5.5 mg/l, albumin <30 g/l.

5. SAN MIGUEL et al [Castelano-Leonés Cooperative Group, 18, 22, 24]: S-phase plasma cells (PC-PI) <3% – score 0, ≥3% – score 2; β_2M <6 mg/l – score 0, ≥6 mg/l – score 1; ECOG performance status <3 – score 0, ≥3 – score 1; age <69 years – score 0, ≥69 years – score 1. The sum of scores gives three stages: stage I – score 0; stage II – score 1–3; stage III – score 4–5.

6. OSS i. e. Olomouc Staging System [3, 19]: stage 1 – ("low risk") serum β_2M <6 mg/l, TK <10 I.U.; stage 2 – ("intermediate risk") β_2M ≥6 mg/l and/or TK 10–20 I.U.; stage 3 – ("poor risk") serum TK ≥20 I.U.

Results

The analysis confirmed that the clinical staging system according to DURIE-SALMON [7] applied in the group of 270 patients treated by conventional chemotherapy divided the patients into three statistically quite different prognostic groups (stage I–III) and two substages (A and B) with significantly different medians and curves of overall survival (OS) (Tab. 1, Fig. 1). Statistical analysis dealing with the staging system according to BATAILLE et al [15, 16] proved in the group of 234 MM patients marked prognostic differences with regard to medians and curves of OS, except a missing difference between the stage 2 ("intermediate") and 3 ("high risk"). A certain disadvantage of this classification system is the concentration of majority of patients in stage 1 ("good risk") (Tab. 1, Fig. 1). Prognostic analysis dealing with the stratification

Table 1. Results of stratification of MM patients analyzed at diagnosis before initiation of therapy according to criteria of 6 selected clinical staging systems

Staging system	No. of cases	Stage	n	(%)	OS median (months)	Log rank test (p<0.05)
Durie-Salmon (15)	270	I	42	(16)	77	0.027, 0.001, 0.001
		II	111	(41)	41	
		III	117	(43)	15	
		A	203	(75)	44	0.001
		B	67	(25)	11	
Bataille R, et al. (3, 4)	269	1	140	(52)	69	0.001, 0.001, 0.192
		2	83	(31)	24	
		3	46	(17)	11	
SWOG (31)	269	1	33	(12)	76	0.017, 0.001, 0.001, 0.001, 0.005, 0.027
		2	92	(34)	63	
		3	108	(40)	21	
		4	36	(13)	8	
San Miguel JF, et al. (38)	121	1	21	(17)	x	0.06, 0.001, 0.002
		2	76	(63)	32	
		3	24	(20)	6	
OSS (42, 44)	186	1	72	(39)	69	0.001, 0.001, 0.001
		2	67	(36)	25	
		3	47	(25)	5	
IPI (20, 21)	270	1	57	(21)	77	0.01, 0.001, 0.005
		2	84	(31)	31	
		3	129	(48)	20	

SWOG – South West Oncology Group, IPI – International Prognostic Index, OS – overall survival, x – overall survival median not reached at the time of statistical analysis

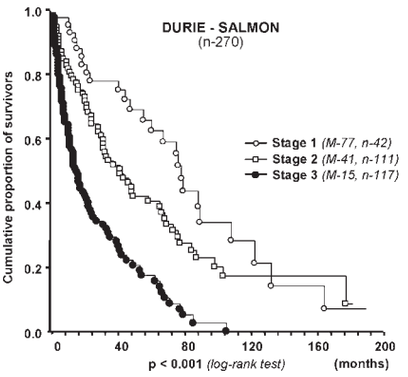
system according to SWOG [17] showed, that also our group of MM patients could be stratified into 4 prognostically different groups (stages 1–4) with significantly different OS medians and survival curves (Tab. 1, Fig. 1). Statistical analysis of 121 patients using the scoring system according to SAN MIGUEL [18] proved this system to be highly advantageous despite a limited number of patients and rather short time of 5 years follow up after initiation of the study, as supported by differences in OS medians (but still not evaluable duration of OS stage 1) and quite different course characteristics of OS curves of stages 1–3 (Tab. 1, Fig. 1). Statistical analysis of the stratification system OSS published in previous studies [3, 19] and based on the evaluation of serum levels of β_2M and TK proved in a large group of 186 MM patients an excellent stratification capacity with regard to prognostic prediction supported by a markedly different lengths of OS medians and course characteristics of survival curves (Tab. 1, Fig. 1).

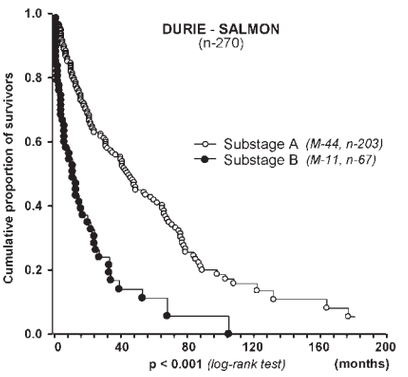
Analysis of applied IPI according to IMWG [13, 14] in the group of 270 patients confirmed the stratification capacity of this system by division of patients into three prognostically different groups. However, differences in OS median of patients at stages 2 and 3 ("intermediate and high risk") were not significant (31 vs. 20 months) (Tab. 1). Rather ambiguous was comparison of initial phases of course characteristics of survival curves of stages 2 and 3 with minimal course differences during first 25 months after diagnosis (Fig. 1), although overall differences between stages 1–3 of the disease were statistically significant.

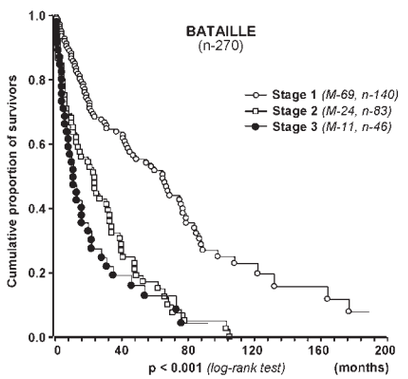
Graphical comparison of OS median length in individual stages of disease progression showed significant differences in prognostic stratification of patients, i.e. groups with "good", "intermediate" and "high", eventually "the worst risk". It is documented that the group with the longest OS median, i.e. stage 1 – "good risk" of 77, 77 and 76 months not usually requiring an immediate initiation of the therapy, was best stratified using the staging system according to D-S, IPI (IMWG) and SWOG and represented 16%, 21% and 12% from our analysed group (Fig. 2). A high risk group, i.e. stage 3 – "high" risk with the lowest OS median of 5 and 6 months with significant statistical difference from the stage 2, i.e. "intermediate" risk, was best stratified by criteria of OSS and the scoring system according to San Miguel comprising 25% and 20% of patients under analysis. It could identify also stage 4 of the staging system according to SWOG, defining the "worst risk" group of patients with OS median of only 8 months, which comprised only 13% of patients in the group under our analysis (Tab. 1, Fig. 2).

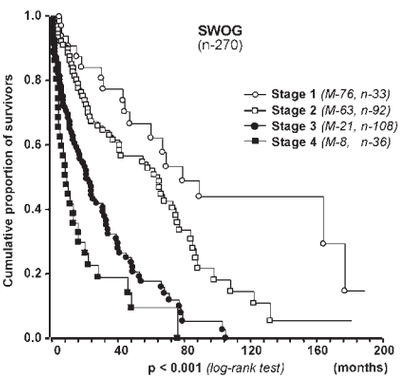
Discussion

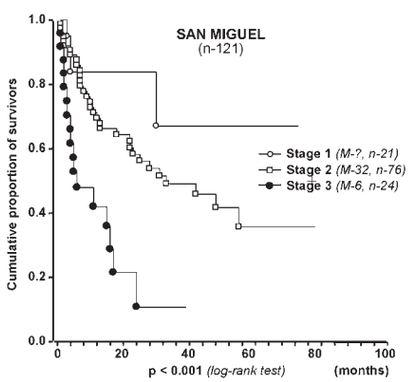
Efforts of effective classification of MM patients into prognostically different groups have been made for over 40 years. Initial stratification systems divided patients into two prognostically different groups ("good and poor risk") on the basis of parameters reflecting mainly tumor size and involvement of renal function, namely the systems of CALGB, NCI, SECSG, ALGB and British MRC [2, 5, 6, 9, 10]. Decisive for MM stratification was the introduction of clinical staging system according to Durie-Salmon classifying patients into 3 stages and 2 substages using the commonly available criteria of a standard diagnostic MM algorithm [7]. An easy practical applicability of this staging system as well as its very good relation to prognosis account for the fact that this system has been widely used as a standard for the period of conventional chemotherapy. Later on, due to the gradually revealed drawbacks of this system, namely the insufficiently defined and subjective evaluation of bone involvement, exclusion of condition of renal function from basic criteria and a certain rigidity of the system when the criterion of initial bone involvement does not allow a

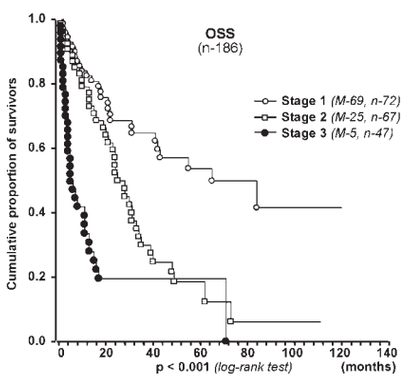












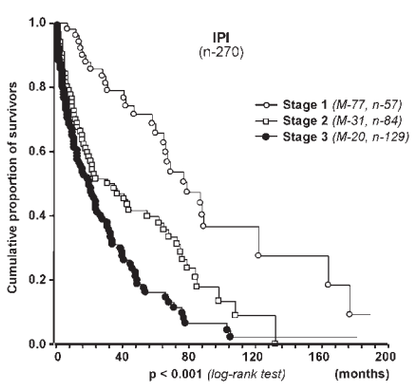


Figure 1. OS curves of patients with multiple myeloma plotted according to Kaplan-Meier and disease phase (stage 1–3 eventually 4, respectively substages A-B) determined using staging system according to DURIE-SALMON [7], BATAILLE et al [15, 16], South West Oncology Group [SWOG; 17], SAN MIGUEL et al [18], Olomouc Staging System [OSS; 3, 19] and IPI (International Prognostic Index) recommended by IMWG [International Myeloma Working Group; 13, 14], M – median of overall survival, n – number of patients.

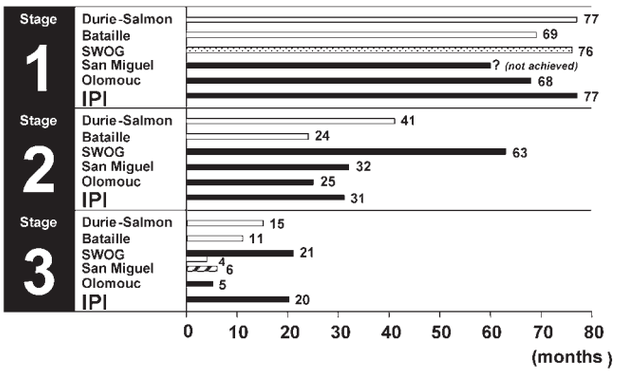


Figure 2. Graphical comparison of medians of overall survival (OS) in stages 1–3 (eventually 4 according to SWOG) in the group of 121–270 MM patients analyzed at diagnosis before therapy initiation and divided by means of staging systems according to DURIE-SALMON, BATAILLE et al, SWOG (South West Oncology Group), SAN MIGUEL et al, staging system OSS (Olomouc Staging System) and IPI (International Prognostic Index).

flexible detection of therapeutic results (remission/plateau, progression/relapse), missing consideration of biological characteristics of MM [3, 11, 24] and particularly reduced prognostic significance of this system in HD-therapy and ASCT [11, 12], generated the efforts for development of a new MM stratification system eliminating the above drawbacks of staging according to D-S. Most newly introduced stratification systems were based on the evaluation of the most important factor of MM, namely the serum level of β_2-microglobulin as the major staging criterion and consideration of some of newly discovered and β_2M independent prognostic factors (PF) related to internal biological properties of myeloma cells, or to reaction of microenvironment of the bone marrow and/or the whole organism to the presence of neoplastic process. Concepts of novel stratification systems were based on the intent to develop a simple, practical, universal and available system. Other systems considered the newly discovered prognostically significant and independent criteria that displayed, however, a complicated applicability thus limiting their practical use [13, 14]. Criteria of over 30 stratification systems [3] developed during the last 20 years comprised prognostic factors (PF) related to proliferation of myeloma cells, i.e. labeling index, Ki_{67} index and serum level of thymidine kinase [11, 23, 25–27], morphologic characteristics of myeloma cells [11, 28, 29], chromosomal aberrations found by FISH method particularly of chromosome 13 [11, 22, 30, 31], levels of cytokines, e.g. sIL-2, sIL-6 a sIL-6R [11, 22, 32–34], markers of bone resorption [11, 22, 24] and factors expressing organism's response to the presence of myeloma tissue, i.e. performance status, albumin, CRP, α_1-antitrypsin, LDH [1, 11, 16, 20, 32] and methods allowing a more sensitive examination of skeleton involvement, e.g. MR, CT, FDG/PET and MIBI (20, 22, 24), and also the results of methods of molecular biology including the assessment of primary forms by means of IgH translocations and cyclin $D_{1\text{-}3}$ expression [35], or tumor tissue sensitivity to chemotherapy. Innovation of standard staging systems was supported by the fact that the use of several new PF allows further subclassification of patients into prognostically different groups within the applied staging systems, e.g. a classical system according to DURIE-SALMON combined with the system D-S PLUS adding the result obtained from MR and FDG-PET [20] or platelet count [4]. The efforts of a complex detection of various prognostic aspects of MM resulted in elaboration of new scoring systems [36]. It should be mentioned that these newly proposed staging systems are not widely used in clinical practice.

The present study focused on comparison of staging system according to D-S as a "golden standard", three staging systems based on the evaluation of serum levels of β_2M and albumin (system according to BATAILLE, SWOG and IPI/ISI), and two staging systems comprising criteria of proliferation properties of myeloma cells, i.e. staging system according to SAN MIGUEL and OSS. Our analysis proved an excellent prognostic reliability and practical applicability of the system according to DURIE-SALMON in the group of patients treated by conventional therapy. We proved an easy and rapid applicability of systems according to BATAILLE, SWOG, IPI and OSS based on only 2 methodologically easily available laboratory criteria. With regard to detection of patients of stage 1, i.e. "low risk" with very favourable prognosis and according to the actual therapeutic doctrine as well as according to supporters of the predominant approach "wait and see" postponing initiation of chemotherapy to the period of progression, most suitable were the systems according to D-S, SWOG, IPI and evidently that according to SAN MIGUEL. With respect to detection of a cohort of high risk patients with short overall survival, i.e. stage 3 "high risk" who should be treated by new and more effective therapeutic modalities, including thalidomide and its analogues or bortezomib in induction and pretransplantation phase [20], most effective were the staging systems according to OSS, SAN MIGUEL and SWOG. Out of the limited number of published verifying analyses, SWOG system was found favorable in the study of GMSG [Greek Myeloma Study Group, 37] and some other papers [20, 38].

The application of IPI in our group of patients did not yield optimal results. Out of all 6 analyzed stratification systems, it was found to be the worst in detection of "high risk" patients where patients of stage 3 represented almost one half of persons with a relatively long 20-month OS median; in the original study the OS median reached even 29 months [13, 14]. Unfavorable was also the comparison of initial phases of course characteristics of survival curves of stages 2 and 3 during first 25 months after diagnosis. Discrepancies between the results of our prognostic analysis and conclusions of pilot study is not clear, this might be due to a different method used for determination of β_2M serum levels and evaluation of various epitopes (RIA in our group vs. ELISA); the

original paper did not specify the method used. IPI was critically evaluated also by the paper of WEBER [39] where this system was found insufficient in staging of patients with short survival (~ 1 year) who could benefit from a new intensive therapy. That study found a similar prognostic importance of β_2M serum levels without consideration of albumin. The study of WANG [38] explained the failing stratification using IPI by the fact that its prognostic significance fails in patients with severe disorder of renal function. A relative drawback of IPI is the fact that it considers markers not specific for MM and influenced by numerous associated factors, e.g. comorbidity, simultaneous inflammation, disorder of renal function or nutrition. Favorable validation of IPI was reported in other recent studies recommending this system for worldwide application [38]. The study of LUDWIG et al recorded the relation between higher age and advanced stages of the disease using IPI [40], another study reported a good relation, in contrast to the system D-S, to serum levels of TNF-α and HGF (Hepatocyte Growth Factor), but not to biochemical markers of bone remodelling [41]. The study of CMG (Czech Myeloma Group) proved the importance of IPI for prognosis of patients after HD-therapy with ASCT, especially at stage 3 [12]. Details of results obtained by several studies showed that although IPI validation was found good, differences between OS medians of stages 1 and 2 were not unambiguous, i.e. 53 vs. 43 months [42]. Considerably better discrimination with respect to MM prognosis, i.e. OS of patients with "good, intermediate and poor risk" was achieved by the newly developed system of United Kingdom Medical Research Council Working Party MRC6PI, covering β_2M, age, performance status, urea, blood count and corrected serum calcium, which was made on the basis of multivariation analysis of 999 patients treated by conventional therapy [43].

The present study indicates that patients treated by conventional chemotherapy can be stratified according to the system of DURIE-SALMON together with IPI and/or SWOG to obtain a large experience of practical details necessary for selection of generally practical and acceptable system. We agree with the opinion that IPI is still only a practical and simple alternative to the system D-S [17]. However, it should be taken into account that there is an urgent need of a new stratification system based on criteria expressing internal biological properties and aggresivity of myeloma clone, its sensitivity to therapy and eventually crucial properties of bone marrow microenvironment. A stratification system derived from these claims could represent a basis of a new, target and individual therapy. As the initial diagnosis, stratification and selection of therapy of MM patients have been concentrated in the specialized hematooncologic centres for MM diagnosis and therapy. In this situation previous requirement of a simple staging system [13, 14, 17, 44] appears to be less important. Particularly the important advances recently achieved in MM therapy and aimed at "individual, target therapeutic cocktails" [45] support the postulate of a stratification system considering actual results of cytogenetic and molecular biological methods [22, 30, 31, 35]. Such a constructed, generally acceptable stratification system will result in an optimized therapy, accurate evaluation of individual prognosis and better organization of prospective multicentre randomized trials [46].

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