Myelodysplastic syndromes according to FAB and WHO classification. Single center experience*

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The results of clinical and laboratory observations of 119 MDS patients divided acc. to FAB, and – after excluding RAEB-t and CMML groups – of 95 patients divided acc. to WHO classification are presented. The diagnosis of MDS was based on medical interview, physical examination, blood biochemistry, peripheral blood (PB) and bone marrow (BM) cytomorphology and cytochemistry, trephine biopsy and cytogenetic examination. All hematologic examinations were done according to routine methods. Cytogenetic analyses were carried out on BM cells from 24–48 h cultures in standard conditions. At least 15–20 GTG-banded metaphases were analyzed in every patient.

The survival time (ST) of patients differed significantly between the FAB or WHO groups, with p=0.0004 for FAB and p=0.02 for WHO. The progression to AML was more common in less favorable groups, with p=0.0001 for FAB and p=0.00016 for WHO. The distribution of IPSS prognostic index among the groups showed statistically significant difference (p=0.0004 for FAB, and p=0.0001 for WHO), whereas the distribution of karyotypic abnormalities did not. However, in univariate analysis statistically significant influence on ST showed, beside the both classification systems: cytogenetics, the presence of blasts in PB, age and IPSS index. In multivariate analysis the sole independent prognostic factors were: PB blasts and cytogenetics.

The authors conclude that the WHO classification offers a good prognostic tool for MDS patients. However, the karyotype and the presence of blasts in PB should always be taken into account.

Key words: MDS, WHO classification, FAB classification, cytogenetics, survival time, IPSS

Myelodysplastic syndromes (MDS) were separated from other hematologic malignancies in 1982 by French-American-British Group (FAB) as a group of diseases with distinct hematological parameters, especially cytopenias and dysplasias, and with determined clinical course and prognosis [1]. In spite of worldwide acceptance of this proposal, which allowed a better classification of these sometimes diagnostically difficult syndromes, many reports indicating a need for a more precise definition of some disease symptoms and for changes in classification of MDS types, started to appear soon after its publication [2–5]. Thus, in 1985 a borderline between acute myeloid leukemia M6 (AML M6) and MDS (2), and in 1994 a basis for differential diagnosis of chronic myeloid leukemia (CML), atypical chronic myeloid leukemia (a-CML), and chronic myelomonocytic leukemia (CMML) were established [6, 7].

The most discussed points were: a position of CMML and RAEB-t (refractory anemia with excess of blasts) among myelodysplastic syndromes and a relation between mono- and multilineage dysplasia in RA (refractory anemia). The classification system of MDS, published in 1999 as a part of WHO classification of hematologic neoplasms, suggested a solution for the above mentioned questions by a lowering of the percentage of bone marrow (BM) blasts required to diagnose AML to 20% [8, 9], which resulted in joining RAEB-t to AML group. CMML was excluded from MDS and localized in a new group of hematologic malignancies, MDS/MPS (myelodysplastic/myeloproliferative syndromes). This group includes diseases showing features of dysplasia, as well as

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myeloproliferation. A subtype of MDS – RCMD (refractory cytopenia with multilineage dysplasia), proposed in 1995 by ROSATI et al, was also created [10].

The cytogenetics of BM cells was in the last decade determined as an independent prognostic factor in MDS. According to the proposal of GREENBERG et al in 1997, BM cells karyotypes were divided in three groups: good (G), intermediate (I) and poor (P) prognosis karyotypes, and incorporated into International Prognosis Scoring System (IPSS) [11].

In the present paper we intended to verify the value of FAB and WHO classifications, as well as that of cytogenetics, in our single center group of patients.

Material and methods

Patients. 120 consecutive patients hospitalized and/or treated in an out-patient service from July 1992 to June 2004 in Hematology Department, Medical University in Wroclaw, were subsided to analysis. The diagnosis of MDS was based on medical interview, physical examination, blood and bone marrow cytomorphology and cytochemistry, blood biochemistry, cytogenetic examination and trephine biopsy. Patients were treated according to standard protocols for MDS.

The patients were classified according to FAB and, after WHO classification was published, also according to its criteria. They were also additionally classified according to cytogenetics. The patients karyotypes were divided in three IPSS types; normal karyotype, as well as 5q-, 20q-, and -Y as a sole changes, were determined as good prognostic cytogenetic factor (G), -7 and 7q-, alone or with other aberrations, as well as complex karyotype were determined as poor prognostic factors (P), and remaining karyotypes – as intermediate ones (I) [11]. On the basis of clinical and laboratory data IPSS prognostic indicator was calculated for every patient.

All results of laboratory examinations here presented refers to the time of diagnosis.

Methods. Peripheral blood (PB) and bone marrow (BM) cytomorphology, BM cytochemistry and PB biochemistry were done using routine methods. Trephine biopsy was performed with a Yamshidi type needle at the posterior illiac spine.

Cytogenetic examinations were based on BM cells. Cell cultures were carried out at 37 °C and 5% CO_2 for 24 and 48 h, according to the methods previously described [12]. At least 15–20 GTG-banded metaphases were analysed according to International System for Human Cytogenetic Nomenclature (ISCN) 1995 [13]. Fluorescence in situ hybridization (FISH) with α-satellite and whole chromosome painting probes was used to resolve complex karyotypes or hidden aberrations.

Statistical analysis. For each parameter (age, survival, etc.) in different FAB and WHO groups mean, median and standard deviation (SD) were calculated. The means of these parameters were compared by one-way analysis of variance (ANOVA). For groups with unhomogenous variance Wilcoxon rank test was used (homogeneity of variance was verified by Bartlett test). The evaluation of discrete parameters distribution was done by chi-square test with Yates correction or, if the expected value was less than 5, by Fisher exact test. Survival time curves were determined using KAPLAN-MEIER estimation method [14], and compared in pairs using log-rank test. $p \leq 0.05$ was acknowledged as statistically significant. The multivariate analysis was carried out with Cox proportional hazard regression model [15]. The analysis was performed using statistical program EPI INFO Ver. 3.2 (dated 04.02.2004).

All procedures were approved by the local Bioethical Committee and were carried out after informed consent of patients.

Results

Among 119 patients with MDS, 51 women and 68 men, 34 fulfiled the criteria for refractory anemia (RA), 13 for refractory anemia with ringed sideroblasts (RARS), 38 – refractory anemia with excess of blasts (RAEB), 17 – RAEB in transformation into AML (RAEB-t) and 12 – chronic myelomonocytic leukemia (CMML). Five patients remained unclassified. Hematological, cytogenetic and some clinical data of patients classified according to FAB are shown in the Table 1. As may be seen, men prevailed, especially in RAEB and RAEB-t groups. Median age was similar in all groups. Median Hb concentration was lowest in RARS, and highest in CMML. Difference between the 5 groups was statistically highly significant.

Median WBC count was lowest in RAEB and highest in CMML. Only 1 patient with WBC 15.2×10^9/l suited the criteria for proliferative type of CMML. A shift to immature cells in granulocyte lineage was found in BM of a half of CMML patients. Mean and median granulocyte counts of the groups did not differ significantly, being lowest in RAEB and highest in the RAEB-t and CMML groups.

The platelet count showed a great dispersion in each group. The median count was the highest in RARS, the lowest in RAEB and RAEB-t groups, with a borderline statistical significance. Anemia was encountered in all RA, RARS and RAEB-t patients and absent in only single patients of the remaining groups. Neutropenia was found in about 60% of patients in 1–4 groups, and in the minority of patients with CMML Thrombocytopenia was less common than neutropenia, the least in RARS group (Tab. 1). Analysis of bone marrow (BM) and peripheral blood (PB) blastosis showed statistically highly significant differences. In BM the highest percentage of myeloblasts was in RAEB-t, followed by RAEB and CMML. In PB the occurrence of myeloblasts was incidental, except for RAEB-t.

Among RAEB-t patients we compared those classified on the basis of BM blastosis (BM subgroup = 10 pts.) and those classified on the basis of PB blastosis (PB subgroup = 7 pts.).

Table 1. Clinical, hematological and cytogenetic data of MDS patients classified according to the FAB types

	All pts.	1 RA	2 RARS	3 RAEB	4 RAEB-t	5 CMML	p
Patients number (N)	114	34	13	38	17	12	–
Sex (F/M)	50/64	17/17	6/7	15/23	6/11	6/6	NS
Age:							
ME	63.5	63.5	66.0	63.0	63	65.0	NS
range	20–79	24–79	39–76	30–79	20–77	41–74	
Haemoglobin [g/L]							
ME	90,9	90.4	78.0	93.0	87.0	106.5	0.00017
range	39.0–158.0	39.0–128.0	54.0–109.0	58.0–113.0	47.0–106.0	81.0–158.0	
Leucocytes [x10^9/L]							
ME	3.8	3.5	3.6	3.2	3.8	6.35	NS
range	0.8–15.2	1.4–11.1	1.9–15.2	0.8–15.1	0.9–7.6	1.8–15.2	
Neutrophils [x10^9/L]							
ME	1.83	1.95	1.75	1.3	2.35	2.3	NS
range	0.1–8.0	0.65–8.0	0.87–7.5	0.23–7.8	0.10–5.0	1.8–5.0	
Platelets [x10^9/L]							
ME	96.5	111.0	192.0	61.0	93.0	123.0	0.06
range	2.0–723.0	11.0 - 723.0	39.0–479.0	2.0–403.0	5.0–312.0	6.0– 235.0	
Medullary blasts [%]							
ME	5.0	1.00	1.0	9.5	20.5	6.0	0.0000
range	0.0–26.0	0.0–5.0	0–4.0	5.0-17.5	3.0–26.0	0–26.0	
Peripheral blasts [%]							
ME	0.000	0.000	0.000	0.000	5.0	0.000	0.0000
range	0–20.0	0–3.0	0	0–12.0	0–20.0	0–4.0	
Incidence [N(%)] of:							
anaemia	110(97)	34	13	36	17	10	0.03
neutropenia	70(61.4)	22	8	27	10	3	0.04
thrombopenia	63(55.2)	17	3	27	11	5	NS
Dysplasia (N) of:							
erythrocytes	91	31	13	27	15	5	NS
neutrophils	53	15	4	19	11	4	NS
platelets	38	13	5	13	6	1	NS
Cytogenetics (N =110)							1 : 4=0.001
Good (G)	58	22	8	21	3	4	2 : 4=0.02
Intermediate (I)	21	7	3	3	4	4	3 : 4=0.01
Poor (P)	31	5	2	11	10	3	3 : 5=0.07
IPSS Index (N=102)							
Low	9	5	3	1	0	0	
Intermediate-1	50	25	6	12	2	5	0.0004
Intermediate-2	25	3	0	14	4	4	
High	18	0	0	5	11	2	
Survival [mo]							
ME	24.0	36.0	45.0	17.0	19.0	29.0	0.0004
range	2.0–226	15.0–226.0*	32.0–72.0*	2.0–65.0	6.0–60.0	10.0–88.0	
Transition to AML (N/91)	32/91	2	0	10	17	3	0.0001

*majority surviving, F – female, M – male, ME – median, N – number

These subgroups differed significantly as to BM blasts percentage (p=0.0006), and at the limit of statistical significance as to PB blasts percentage (p=0.07). The median survival time in these subgroups did not differ significantly. However, it was shorter in PB subgroup (16.5 mo), than in BM subgroup (22.0 mo). IPSS index differed significantly (p=0.0028) between the subgroups. Poor prognostic karyotype was found in 5 among 7 patients of the PB group and in 5 among 10 patients of the BM group.

Erythroid dysplasia was most common in RA and RARS. The differences in the occurence of dysplasia of erythroid, as well as that of other cell lineages were not statistically significant.

Cytogenetic analyses revealed prognostically good (G)

karyotype in 58 among 109 examined patients, poor (P) in 31 and intermediate (I) in 20 patients. G karyotype was found in nearly 2/3 RA patients, while P karyotype was most common in RAEB (11/35) and in the RAEB-t (10/17) groups. No statistically significant differences were found among different FAB group as a whole, but they were revealed between single groups (Tab. 1).

The distribution of the IPSS index among the groups was highly statistically significant (p=0.0004). In prognostically favourable FAB groups high risk (H) IPSS index was absent, and inversely – in groups with unfavourable prognosis L-type (low-risk) IPSS index was not found.

The information concerning survival time was not available in 28 patients. Survival time, known in 91 patients, was the shortest in RAEB and RAEB-t and the longest in RARS and RA (p = 0.0004). Survival time curves, according to FAB classification, are shown in the Figure 1a.

The transition to AML also differentiated FAB groups with a statistical significance (p=0.0001). It was found in all patients with RAEB-t, and in no patients with RARS. In RA, CMML, RAEB groups it occurred in about 6, 25, and 26%, respectively.

Ninety five patients were reclassified according to WHO criteria, after exclusion of RAEB-t and CMML groups. Because of low number of patients in RA and RARS groups, and the similarity of data, they were analyzed jointly, as a single group. RCMD group included 31 patients, RCMD-RS – 8, RAEB-1 – 19, and RAEB-2 – 27. Only one person, who was classified in RARS group in FAB analysis, disclosed 5q-syndrome and another two remained unclassifiable.

Table 2 presents the data of patients divided according to WHO classification. There was no statistically significant difference between sex distribution and median age. Hb concentration, leucocyte, neutrophil and platelet counts were the most favourable in RA+RARS group, with significant differences of Hb, platelet and neutrophils values. Very highly statistically significant difference was present among the groups in medullary and peripheral blood blastosis, which was the highest in the RAEB groups.

Anemia was present in nearly all patients (98%). Neutropenia, as well as thrombocytopenia, were not observed in RA+RARS group, but in the remaining groups neutropenia was common, especially in RCMD and RCMD-RS. Thrombocytopenia was somewhat less common. Highly significant differences of these parameters were found in between the WHO groups. Dysplasia of the erythroid cell line was commonly seen in all groups, without statistical difference. Dysplasia of the other cell lines was less common.

Favorable karyotypes were most common in RA-RARS and RCMD groups, the least common in RAEB-2, and the unfavourable ones – inversely. There was no statistically significant difference in the distribution of cytogenetic types among the groups as a whole. However, statistically significant differences were found between RA+RARS and RAEB-2 (p=0.0004), and between RCMD and RAEB-2 (p=0.0005), and some other were at the statistical limit, as shown in the Table 2.

IPSS prognostic index distribution showed highly statistically significant differences among the groups taken as a whole (p=0.0001). In the prognostically favourable groups the IPSS index above 1.5, and in the unfavourable ones its value below 1.5 were never found.

Survival time was the longest in RA+RARS group, the shortest in RAEB 1 and 2 (p=0.02) (Fig. 1b). Progression to AML strongly differentiated WHO groups: it was the most common in RAEB-2, followed by RAEB-1, and absent in RA+RARS group (p=0.00016).

Independently from the division of MDS patients in the FAB and WHO groups, a dependence of survival time (ST) on karyotype of BM cells (Fig. 1c) and on IPSS type (Fig. 1d) was calculated and presented by Kaplan-Meier curves. In both cases statistically significant difference was obtained. The dependence of ST on blastosis was also determined, ST of persons without blasts in PB was 39.7 months (SD 36.3) and those with PB blastosis 21.3 (SD 16.5), these values being statistically significantly different.

In univariate analysis, without a division of patients into groups, statistically significant ST determining factors were found to be: 1. WHO classification (p=0.00003), 2. FAB classification (p=0.00017), 3. karyotype of BM cells (p=0.00116), 4. presence of blasts in PB (p=0.00179), 5. age (p=0.00965) and 6. IPSS (p=0.0177). On the limit of statistical significance was the presence of blasts in BM (p=0.09). Sex was not found to be a ST determining factor.

Multivariate analysis, however, revealed 2 independent factors influencing survival: presence of blasts in PB (p=0.00657) and karyotype (p=0.0311).

Discussion

Our analysis showed that FAB classification significantly differentiated MDS patient groups as to survival time and progression to AML. However, after CMML and RAEB-t exclusion, the groups distinguished by WHO classification differed from each other even more significantly, which proves that the proper classification criteria were applied in WHO system.

The exclusion of RAEB-t from MDS seems to be right on the basis of our observation, that all RAEB-t patients transformed to AML. The objections of some authors, concerning this exclusion, were caused by different biology of AML blasts versus MDS blasts, as expressed by higher activity of caspase 3, an apoptotic marker, and higher level of PCNA, a proliferation marker, in RAEB-t than in AML. The values of these two factors in RAEB-t were found to be similar to those in other MDS types [16].

Some authors suggested that in WHO classification the importance of the presence of blasts in PB, without BM blastosis, should be more stressed, because this often denotes worse prognosis than BM blastosis, what was seen also in our

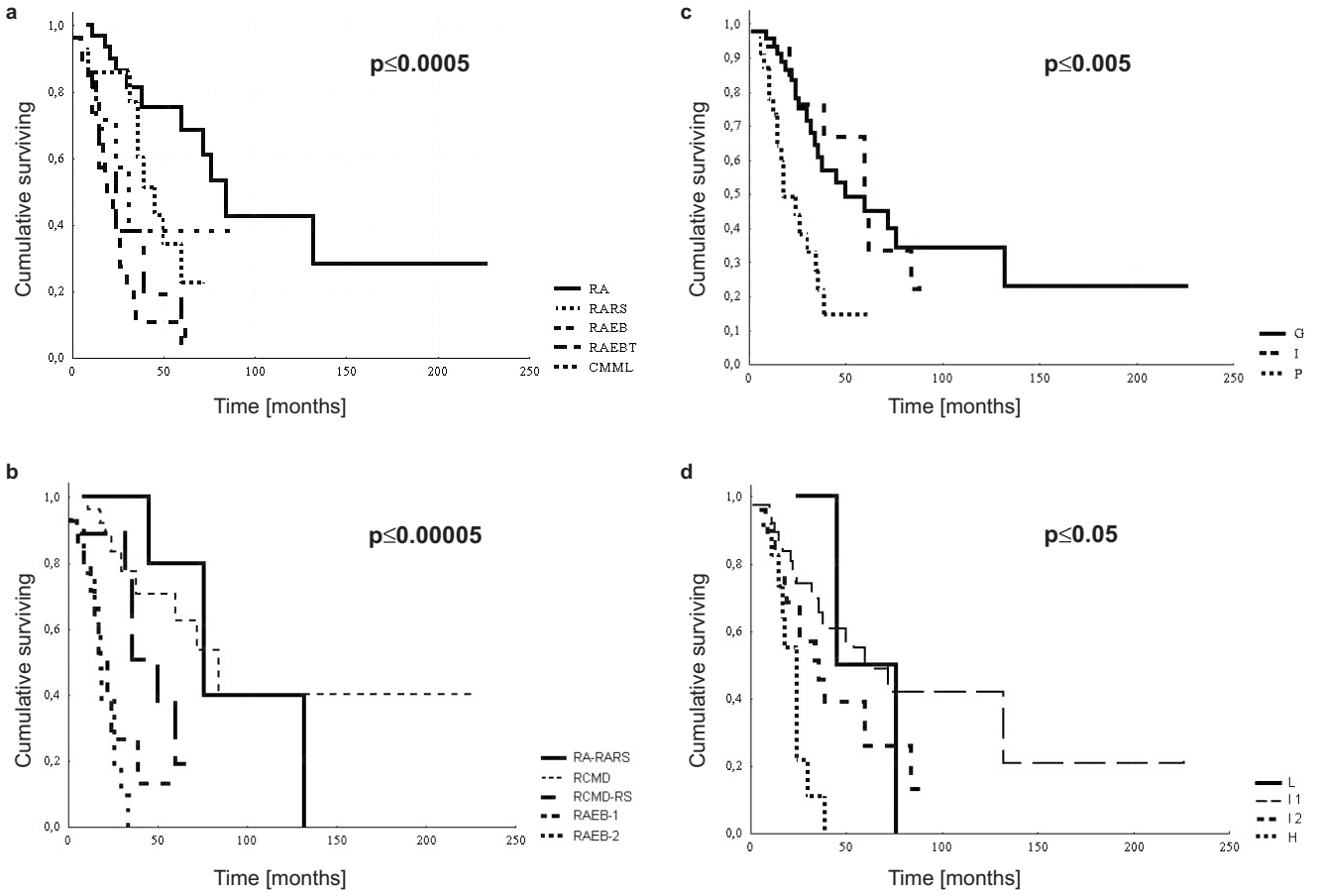

Figure 1. a) Kaplan-Meier survival time curves according to FAB classification; b) Kaplan-Meier survival time curves according to WHO classification; c) Survival time curves according to cytogenetic groups – good (G), intermediate (I), poor (P). d) Survival time curves according to IPSS groups.

material of RAEB-t subgroup based on PB blasts. These cases are often characterized by unfavorable cytogenetic changes [17, 18]. The presence of blasts in PB was in our material an independent prognostic factor.

The introduction of RCMD group to the new classification is worth of attention. This group comprises cases of more than one lineage cytopenia and is related with shorter survival than that in RA or RARS.

The exclusion of CMML from MDS and the creation of MDS/MPS group is also relevant. Many observations describing a simultaneous existence of dysplasia and chronic proliferation in MDS and MPS are in favour of it [19, 20]. However, there remain still some cases difficult to classify, e.g. our patient, who developed thrombocytopenia at the age of 57 years, then 5 years later – CMML, and after next 2 years – RAEB, which transformed to AML-M2 (unpublished observation).

In our material only one patient had 5q-syndrome. The occurrence of this syndrome is probably population-dependent. Some authors described single cases of 5q-, some others – up to 20% cases among all MDS patients [21–23].

General population differences in MDS were stressed by OGUMA et al [24]. Their observations, contrary to European data, showed that the qualitative changes in megakaryocytic and granulocytic lineages were more important for prognosis in Japanese population, than the quantitative ones. BALDUINI et al [25] analyzed 8 prognostic systems created following FAB classification and concluded that those proper for one population were not necessarily suitable for the others.

The significance of cytogenetics for the prognosis of patients with MDS is very important, what was already stressed nearly twenty years ago and developed later [26, 27]. In 1997 GREENBERG et al, besides of prognostic classification of karyotypes, proposed a system (IPSS = International Prognostic Scoring System), comprising also the percentage of blasts in BM, and the number (1–3) of cytopenias, i.e. the factors taken into account in the majority of earlier MDS prognostic systems [11]. In our material the distribution of IPSS index values distinguished with statistical significance the groups of MDS patients classified according to FAB and WHO. There was not statistical significance in the distribution of prognostically different karyotypes (G, P, and I)

Table 2. Clinical, hematological and cytogenetic data of MDS patients classified according to the WHO types

	All pts.	1 RA+RARS	2 RCMD	3 RCMD-RS	4 RAEB-1	5 RAEB-2	p
Patients number (N)	95	10	31	8	19	27	–
Sex (F/M)	40/55	2/8	14/17	4/4	9/10	11/16	NS
Age:							
median (ME)	65.0	72.5	61.0	63.0	69.0	63.0	NS
range	24–83	31– 83	24–79	47–71	33–79	30–80	
Haemoglobin [g/L]:							
ME	88.0	104.5	90.0	74.5	98.0	86.0	0.015
range	39.0 –129.0	69.0–128.0	39.0–12.09	54.0–86.0	68.0–113.0	48.0–122.0	
Leucocytes [x10^9/L]:							
ME	3.55	5.75	3.2	3.25	4.0	3.45	NS
range	1.0–15.1	4.2–15.2	1.0–9.8	1.9–5.6	1.1–15.1	1.6–15.1	
Neutrophils [x10^9/L]:							
ME	1.73	3.1	1.6	1.78	1.15	0.75	0.01
range	0.12–5.25	2.5–6.9	0.46–5.25	0.5–3.45	0.29–5.2	0.12–3.8	
Platelets [x10^9/L]:							
ME	87.5	223.0	90.0	115.0	53.0	53.5	0.008
range	3.0–728.0	148.0–728.0	11.0–333.0	25.0–207.0	15.0–429.0	3.0–403.0	
Medullary blasts[%]:							
ME	3.0	0.000	1.25	2.5	7.25	11.0	0.0000
range	0–17.0	0–1.0	0–4.5	0–3.0	5.0 - 9.5	10.5–17.0	
Peripheral blasts [%]:							
ME	0.000	0.000	0.000	0.000	0.000	2.5	0.0000
range	0–12	0	0–2.0	0	0–4	0–12	
Incidence [N/N(%)] of:							
anemia	94/95(99)	10/10	31/31	8/8	18/19	27/27	NS
neutropenia	61/95(65)	0	25	7	12	17	0.00009
thrombocytopenia	55/95(58.5)	0	20	3	13	19	0.0008
Dysplasia [N/N(%)] of:							
erythrocytes	76/78(97)	9/9	27/27	6/6	13/14	21/22	NS
neutrophils	42/77(56)	3	14	2	7	16	NS
platelets	35/77(45)	1	14	3	7	10	NS
Cytogenetics							1 : 5 = 0.004
(N=92):							2 : 5 = 0.005
Good (G)	54	8	19	3	12	12	1 : 2 = 0.08
Intermediate (I)	14	1	6	3	3	1	1 : 3 = 0.09
Poor (P)	24	1	5	2	4	12	4 : 5 = 0.07
IPSS index (N=87)							
Low	10	7	2	0	1	0	
Intermediate-1	47	2	23	6	9	7	0.0001
Intermediate-2	23	0	4	2	7	10	
High	7	0	0	0	0	7	
Survival							
ME [months]	24	45	32	43	18.5	18.0	0.02
range	5–226	9–76*	9–226*	8–65	6–60	5–65	
Transition to AML (N=86)	18	0	2	1	6	9	0.00016

*majority surviving, N – number, ME – median, F – female, M – male

among the FAB or WHO groups of patients as the whole, and in their relation to survival. However, in Cox multivariate analysis of the whole material, not divided into groups, cytogenetics appeared, beside the presence of blasts in PB, the most important independent factor influencing survival time. This suggests the need for taking into account the results of cytogenetic examination in prognosing an individual clinical course of MDS, as well as in choosing therapy options, what was also stressed by other authors [28, 29]. CERMAK et al [28] investigated a group of over 100 patients

with RCMD and showed that a transplantation of hematopoietic cells in early stages of the disease was profitable only for those with unfavourable cytogenetic changes.

Concluding, the WHO classifying system is very reliable in diagnosing myelodysplastic syndromes and in therapy planning, but the results of cytogenetic examination should always be taken into account [11, 28–30].

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