Original Articles

Pretherapeutic Identification of High-Risk Acute Myeloid Leukemia (AML) Patients from Immunophenotypic, Cytogenetic, and Clinical Parameters

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Background: The goal of this study concerned the pretherapeutic identification of high-risk acute myeloid leukemia (AML) patients by data pattern analysis from flow cytometric immunophenotype, cytogenetic, and clinical data.

Methods: Sixty-seven parameters of AML patients at diagnosis were classified for predictive information by algorithmic data sieving using iteratively self optimizing triple matrix data pattern analysis (http://www.biochem.mpg.de/valet/classif1.html).

Results: Pretherapeutic predictive values for nonsurvival within five years and two years were 100.0% and 83.2%, respectively, compared to 13.9% and 47.4% for the prediction of survival at five years and two years, respectively. At diagnosis, five-year nonsurvivors showed increased patient age and higher concentration of cells in the analyzed specimen, as well as increased levels of % CD2, CD4, CD13, CD36, and CD45 positive AML blasts. Two-year nonsurvivors were characterized by a data pattern of increased patient age and levels of % CD4, CD7, CD11b, CD24, CD45, TH126, and HLA-DR positive AML blasts and decreased levels of % CD1, CD65, CD95, and TC25 positive AML blasts. Cytogenetic abnormalities were not selected for the optimized discriminatory data patterns.

Conclusions: The comparatively accurate pretherapeutic identification of high-risk AML patients may prove useful for the development of individualized therapy protocols in stratified clinical patients groups. Cytometry Part B (Clin. Cytometry) 53B:4–10, 2003. © 2003 Wiley-Liss, Inc.

Key terms: acute myeloid leukemia (AML); predictive medicine; personalized medicine; clinical cytomics; data sieving; medical bioinformatics

Current acute myeloid leukemia (AML) therapy is characterized by an induction chemotherapy followed by a risk-adapted post-remission therapy including autologous or allogeneic hematopoietic stem cell transplantation (SCT). Despite significant progress, the overall survival of AML patients after therapy remains unsatisfactory (1). Considerable efforts have been made to identify molecular parameters, such as cytogenetic abnormalities (2), mutations (3), or cell surface markers (4–6) as prognostic factors, in an effort to better stratify AML patients for adequate therapy. Prognostic factors represent statistical operators. They describe the overall outcome tendency of stratified patient groups, but no evaluation of disease outcome for individual patients is possible.

When several prognostic factors are analyzed in combination as a data pattern, they may, however, provide individualized disease course prediction or risk assessment. Typical data analysis methods like statistical multivariate analysis require assumptions on the mathematical distribution of the value distributions of factors to be analyzed, outlier values may have to be removed, missing values are frequently substituted by interpolation, or individual patients have to be removed from consideration. Algorithmic data sieving as an alternative is not limited by

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Table 1
Database Parameters

Clinical parameters	Cytogenetic parameters		CD-antigens		
Patient_age	Cytogen	t3_3	CD1	CD36	TH126
Patient_sex	Abnorm	t6_9	CD2	CD38	TC12
zz_mio	del5	t9_11	CD4	CD41	TC25
Leuk	del7	t9_22	CD7	CD42	TDT
LDH	dely	t15_17	CD9	CD45	cyCD3
fit3	mono	abn12	CD10	CD56	HLA-DR
OS	inv3	abn11	CD11b	CD58	
Clinic_nr	tri8	aberr_m	CD14	CD61	
Patient_nr	tri11	inv16	CD15	CD64	
	tri13	elseabno	CD19	CD75	
	tri21		CD20	CD95	
	tri22		CD24	CD96	
	t8_21		CD32	CD117	
	t8_16		CD33	GlyA	
	t1_7		CD34	MPO7	

these considerations (7), the classifiers are suitable for prospective classification of unknown patients in multicenter studies, and standardized classifiers can be developed by consensus.

Patients of the SHG-multicenter studies AML'91 and AML'96 fulfilling the two-year or five-year survival or nonsurvival criteria were included in the subsequent classifications in an effort to provide more specific a priori information on individual AML patients to the clinician.

PATIENTS, MATERIALS, AND METHODS

The clinical, immunophenotypic, and cytogenetic results of 724 AML patients with the last followup in July 2001 were available in a database with 70 data columns (Table 1). Details on the various parameters are provided in the accompanying clinical communication within this supplement (8). Six clinical, 25 cytogenetic and 36 CD-antigen parameters were subjected to CLASSIF1 data pattern analysis (7,9–11). The remaining three parameters clinic_nr and pat_nr served as patient identifier and overall survival (OS) as clinical truth for the predictive classifications.

Data Pattern Analysis

The CLASSIF1 algorithm (7, http://www.biochem.mpg.de/valet/classif1.html) transforms numeric values of database columns into –, 0, or + triple matrix characters. The transformation depends on their position below the lower percentile, between the lower and upper percentile, or above the upper percentile threshold of the respective value distribution for the reference patient group of survivors. Following triple matrix transformation for all database columns, a confusion matrix is established between the clinical outcome survival/nonsurvival and the computer classification survival/nonsurvival. The computer classification is derived by algorithmic data sieving from the database parameters.

The diagonal values of the confusion matrix represent the classification specificity for the prediction of survival for the reference patients and the classification sensitivity for the prediction of nonsurvival. The optimum classification is ideally reached when all samples are correctly classified—that is when the value in each of the diagonal boxes of the confusion matrix is 100% while the values in nondiagonal boxes are 0%. This is typically not the case in the beginning. Iterative learning optimizes the sum of the diagonal values of the confusion matrix by the recording result improvement or deterioration upon temporary removal of data columns, followed by exclusion of nonpredictive columns at the end of the iterative procedure. This leads to the enrichment of the predictive data columns in the disease classification masks. The learning process is routinely performed for the 10%–90%, 15%–85%, 20%–80%, 25%–75%, and 30%–70% thresholds with final selection of the optimum classification result. The disease classification mask for the reference group of patients typically contains a sequence of (0) characters because the majority of values are located between the two percentile thresholds, for example, in the 30%–70% situation. Forty percent of the triple matrix characters are (0), 30% are (–), and 30% are (+). The disease classifier mask for the survivor reference groups contain two triple matrix characters, e.g., (0+) in case the parameter is diminished (–) in nonsurvivors, or (0–) in case of an increase (+) of this parameter in nonsurvivors.

Unknown patients are classified according to the highest positional coincidence of their patient classification mask with any one of the previously learned disease classification masks. A patient is classified with a double classification in case of equal numbers of hits, e.g., for the survivor, as well as for the nonsurvivor, disease classification masks. Double classifications occur for transitional state patients exhibiting borderline parameter patterns between two classification categories. Missing values in the triple matrix pattern or lack of overall information to clearly distinguish the two classification categories are additional causes for double classifications. They represent classification errors.

Table 2A
Classification for 2-Year Survival

	CLASSIF1 classification, 2 year			
Clinical outcome	Pat. (n)	Surv. (%)	Nsurv. (%)	Ambig. class. (n)
Learning set				
2-year survival	89	91.0	9.0	8
2-year nonsurvival	189	67.2	32.8	14
Neg./pos. pred. values (%)	–	38.9	88.6	–
Unknown test set				
2-year survival	61	63.9	36.1	1
2-year nonsurvival	192	55.2	44.8	9
Neg./pos. pred. values (%)	–	26.9	79.6	–
Learning + test set				
2-year survival	150	80.0	20.0	9
2-year nonsurvival	381	61.1	38.9	23
Neg./pos. pred. values (%)	–	47.4	83.2	–
Learning + test set patients	563			
Total patients survival				
2-year survival	159	28.2		
2-year nonsurvival	404	71.8		
Sum	563	100.0		
<2-year still surviving	161			
Total patients	724			

30–70% percentile thresholds, database: DO/REPP37.B14.

All parameters contribute equally to the classification result of an individual patient. The position of the parameters in the disease classification mask corresponds to their location in the database. The CLASSIF1 algorithm does not require assumptions on the mathematical distribution of the classified parameters, no cropping of far outreaching values is performed, and missing values do not have to be substituted. The five-year survivors and five-year nonsurvivors were classified in the same way as just described for the two-year condition.

The initial database contained the data of 724 AML patients. It was a priori split into a learning database comprising the first 425 patients and a test database containing the remaining 299 patients who remained unknown to the learning process. The second database was used to check the classification capacity of the learned classifiers on unknown patients. Two hundred and fifty-seven patients of both databases are still alive, with survival times of less than five years. They were useful for prospective classification.

RESULTS

Certain parameters were excluded from classification because of less than 15% available values, such as lactate dehydrogenase (LDH), leuk, and CD56 for the two-year survival classifications, reducing the number of classified parameters to 64. Similarly, LDH, leuk, FLT3, CD1, CD3, CD41, CD42, CD56, CD58, CD64, CD95, CD117, TH126, and TC25 parameters were not used for the classification in the five-year survivor group, leaving 53 parameters for classification.

Both pretherapy databases were classified for survival and nonsurvival after two years (Table 2A and 2B) and five years (Table 3A and 3B). Further splitting into the three categories 0- to one-year nonsurvival, one- to five-year nonsurvival, and five-year survival provided insufficient separation between the categories (data not shown) and was not further pursued. The two-year nonsurvivors were correctly identified in 88.6% and 79.6% of the cases in the learning and unknown test set, respectively, while the survivors classified with lower values (Table 2A). The entire dataset classified with predictive values of 83.2% for nonsurvival. Around 6% of patients could not be assigned to either one of the classification categories because of double (transitional) classifications (right-most column of Table 2A).

Five-year nonsurvivors were correctly identified with predictive values of 100.0%, with around 2% double classification (Table 3A). The unknown test set classified with a higher sensitivity of 91.5% than the learning set (49.8%). No unknown test set was defined for five-year survivors because of the relatively restricted group of 25 patients with five-year survival.

Table 2B
Disease Classification Masks: 2-Year Survival

	2-year	
Parameters	Surv.	N.surv.
Patient_age	0–	+
% CD1	0+	–
% CD4	0–	+
% CD7	0–	+
% CD11b	0–	+
% CD24	0–	+
% CD45	0–	+
% CD65	0+	–
% CD95	0+	–
% TH126	0–	+
% TC25	0+	–
% HLA-DR	0–	+

Table 3A
Classification for 5-Year Survival

	CLASSIF1 classification, 5-year			
Clinical outcome	Pat. (n)	Surv. (%)	Nsurv. (%)	Ambig. class. (n)
Learning set				
5-year survival	24	100.0	0.0	1
5-year nonsurvival	269	50.2	49.8	6
Neg./pos. pred. values (%)	–	15.1	100.0	–
Unknown test set				
5-year nonsurvival	165	8.5	91.5	2
Learning + test set				
5-year survival	24	100.0	0.0	1
5-year nonsurvival	434	33.4	65.6	8
Neg./pos. pred. values (%)	–	13.9	100.0	–
Learning + test set patients	467			
Total patients survival				
5-year survival	25	5.4		
5-year nonsurvival	442	94.6		
Sum	467	100.0		
<5-year still surviving	257			
Total patients	724			

25–75% percentile thresholds, database: DJ/REPP32.B14.

The disease classification mask (Table 2B) predicts two-year nonsurvival at increased (+) patient age (> 53.8 years, Table 4A), as well as increased frequency of CD4, CD7, CD11b, CD24, CD45, TH126, and HLA-DR positive AML blasts and decreased CD1, CD65, CD95, and TC5 positive AML blasts. The disease classification masks for five-year survival and five-year nonsurvival (Table 3B) predicts nonsurvival at increased patient age (> 51.8 years; Table 4B), higher number of cells, isolated from the analyzed specimen (> 229 × 10^9/l), as well as at increased % CD2, CD4, CD13, CD36, and CD45 positive AML blasts. Discriminatory potential and statistical significance are not strictly linked for a number of parameters (Table 4A and 4B).

The reclassification results for 10 sequential patients of the learning set for five-year survival (clinical outcome = 1, Table 5B) and nonsurvival (clinical outcome = 2, Table 5C) indicate that five-year survivors are correctly classified (= 1) by the CLASSIF1 algorithm. The classification coincidence factors between 0.57–1.00 indicates the degree of positional coincidence of the patient classification mask (Table 5B and 5C) with the selected disease classification mask (Table 5A). Nine of the 10 nonsurvivor patients are correctly identified (= 2) and one patient is erroneously classified as a five-year survivor (=1). The classification coincidence factors for nonsurvivors are between 0.57 and 1.00.

Table 3B
Disease Classification Masks: 5-Year Survival

	>5-year	
Parameters	Surv.	Nsurv.
Patient_age	0−	+
zz_mio	0−	+
% CD2	0−	+
% CD4	0−	+
% CD13	0−	+
% CD36	0−	+
% CD45	0−	+

The comparison of the classification results for five-year survivors (Table 5B) and nonsurvivors (Table 5C) shows that 95.0% of the patients are correctly classified, although identity between the patient and the disease classification masks occurs only in two (patients 100073 and 080055) of the 20 classified patients (10.0%). This indicates a certain independence of the classification from identity with the disease classification mask. Eighteen patterns fulfill the disease classification criteria. The frequency of decreased (–), unaltered (0), and increased (+) characters in the displayed classification masks shifts from 15(–), 34(0), 21(+) (Table 5B) in five-year survivors to 8(–), 10(0), 50(+) (Table 5C) in five-year nonsurvivor patients. The increase of (+) characters and a concomitant decrease of (–) and (0) triple matrix characters is obvious. All parameter values were available in five-year surviving patients (Table 5B), while two values are missing (.) in the five-year nonsurvivors (Table 5C).

The prospective classification of the remaining 257 surviving patients with less than five-year survival time provided individualized five-year nonsurvival predictions for 63.8% of the patients. This is similar to the 65.6% for the retrospective learning and test set analysis of Table 3A. Most of these presently surviving patients—249 of 257 or 96.9%—were classifiable.

DISCUSSION

The essential result of this study concerns the pretherapeutic prediction of five-year and two-year nonsurvival with 100% and 88.6%, respectively, predictive value for a substantial number of 49.8% and 32.8%, respectively, of ultimately nonsurviving patients (Tables 2A and 3A). Survival prediction, in contrast, is unreliable, with predictive values of only 15.1% and 38.9%, respectively.

Table 4
Discriminatory Parameters

Parameter	Survival means ± SEM (n)	Nonsurvival means ± SEM (n)	Statistical significance (Student P)	Percentile values
A. 2-year survival[a]				
Patient_age (y)	45.2 ± 1.4 (90)	52.7 ± 1.1 (210)	<0.001	36.5/53.8
% CD1 pos.	2.24 ± 0.50 (57)	1.22 ± 0.18 (81)	<0.01	0.12/1.54
% CD4 pos.	12.9 ± 1.7 (84)	17.4 ± 1.4 (187)	<0.01	4.02/13.5
% CD7 pos.	16.3 ± 1.8 (96)	17.6 ± 1.5 (202)	NS	5.31/15.9
% CD11b pos.	22.0 ± 2.3 (91)	31.6 ± 1.6 (197)	<0.0025	6.73/21.6
% CD24 pos.	12.3 ± 1.4 (89)	14.8 ± 1.2 (193)	NS	3.84/12.0
% CD45 pos.	82.7 ± 1.7 (89)	85.8 ± 1.2 (193)	NS	78.6/93.0
% CD65 pos.	29.3 ± 2.2 (93)	26.6 ± 1.5 (198)	NS	15.2/37.4
% CD95 pos.	25.9 ± 3.1 (43)	24.6 ± 1.6 (140)	NS	12.5/28.6
% TH126 pos.	54.0 ± 3.0 (57)	53.5 ± 3.0 (79)	NS	37.0/68.9
% TC25	64.2 ± 3.2 (58)	65.2 ± 2.8 (77)	NS	60.0/79.4
% HLA-DR pos.	54.8 ± 2.7 (97)	54.0 ± 2.0 (203)	NS	46.0/70.0
B. 5-year survival[b]				
Patient_age (y)	42.8 ± 2.6 (25)	53.6 ± 0.9 (275)	<0.001	31.4/51.8
zz_mio (10^9/l)	191 ± 50 (25)	387 ± 41 (262)	NS	56/229
% CD2 pos.	7.68 ± 0.99 (22)	9.49 ± 0.79 (263)	NS	3.48/8.86
% CD4 pos.	9.71 ± 2.1 (21)	17.7 ± 1.2 (253)	<0.05	2.51/12.8
% CD13 pos.	36.1 ± 4.8 (25)	51.7 ± 1.5 (275)	<0.0025	15.4/49.6
% CD36 pos.	19.7 ± 3.6 (25)	29.9 ± 1.5 (271)	<0.025	6.52/22.7
% CD45 pos.	79.0 ± 3.4 (21)	86.5 ± 1.0 (261)	<0.025	73.2/87.6

[a]Percentile values are 30–70%.
[b]Percentile values are 25–75%.
NS = not significant.

The selected parameter masks (Tables 2B and 3B) indicate that CD antigens, in combination with patient age and number of isolated cells from the patient sample (zz_mio), are informative for predictions, while no cytogenetic parameters are selected. This is understandable because they occur only in about half of the AML patients (1), which represents a serious disadvantage for individualized classifications. CD antigens, in contrast, are present on all AML blasts. Their apparent information content for individualized disease course predictions prompts the future evaluation of more detailed information. Relative antigen densities, antigen ratios, and relative packing density of antigens on leukemic blast cells have been informative parameters in the individualized classifications of other hematologic malignancies (9) and could be of equal value in AML patients.

The selection of CD antigens by data pattern analysis may prompt the search for AML typical antigen patterns in premalignant myelodysplastic patients for individualized therapeutic approaches during the preneoplastic phase.

Cytogenetic parameters (3), the presence of certain antigens on AML blasts (4–6), but also clinical parameters like patient age (12) and blast counts (13), contain prognostic information. Prognostic factors are of importance for patient stratification in multicenter therapy trials. They are typically characterized by a certain fraction of therapy responders and a fraction of nonresponders (8). Prognostic parameters do, however, not identify nonresponders before therapy.

As shown by the results of the individualized predictive classifications, the pretherapeutic identification of 40% to 60% of the high-risk AML patients in stratified groups (Tables 2A and 3A) seems possible. Predictive classification is therefore of significant clinical interest, provided such predictions are reliably accurate in more than 95% or 99% of the cases, as is shown for five-year nonsurvival in this study (Table 3). It will be possible to check the accuracy of the prospective predictions for five-year nonsurvival, which has been established for the further outcome of patients alive in July 2001.

The comparison of the prognostic stratification (8) with the predictive classifications indicates that only two (CD11b, HLADR) parameters of the predictive data pattern for two-year survival (Table 2B) coincide with OS in the uni- and multivariate data analysis of the same patient group. For five-year survival, %CD4 and %CD13 (Table 3B) are selected by the predictive and prognostic data classification.

It is interesting that a certain number of classification parameters is selected by the data sieving algorithm although the differences of the parameters means for survivors and nonsurvivors are not statistically significant (Table 4). Such parameters may provide nonoverlapping parts of skewed value distributions for the discrimination of certain subgroups of patients. Indications for skewedness of value distributions are nonsymmetrical positions of the percentile thresholds with respect to the parameter means, e.g., CD7, CD24, CD65, and CD95 in Table 4A, and zz_mio and CD2 in Table 4B. The frequently used selection of promising classification parameters exclusively by statistical significance may miss valuable classification information. Algorithmic data sieving, in contrast, screens all parameters for classification potential.

Table 5
Reclassification of the Learning Set for 5-Year Survival

Classification categories		Category abbreviation	Class. coinc. factor	Disease classification masks pat age	zz mio	CD2	CD4	CD13	CD36	CD45
A. Disease classification masks										
5-year survivors		1	1.00	0	0	0	0	0	0	0
				–	–	–	–	–	–	–
5-year nonsurvivors		2	1.00	+	+	+	+	+	+	+
Patient_id	Clinical outcome	CLASSIF1 prediction	Class. coinc factor	Patient classification masks						
B. 5-year survivors										
AML080049	1	1	0.57	0	0	+	0	+	0	+
AML100073	1	1	1.00	0	0	–	0	–	–	0
AML240002	1	1	0.71	0	0	+	0	0	–	+
AML100078	1	1	0.57	0	–	+	+	0	+	0
AML230031	1	1	0.57	+	0	+	0	–	+	–
AML030199	1	1	0.86	0	0	+	0	–	0	0
AML030196	1	1	0.57	–	0	+	+	+	0	–
AML080055	1	1	1.00	–	0	0	–	0	–	0
AML020251	1	1	0.57	0	0	+	+	+	0	0
AML100082	1	1	0.57	–	0	–	+	+	0	+
C. 5-year nonsurvivors										
AML080016	2	2	0.71	+	+	+	+	–	+	–
AML300022	2	2	0.57	+	0	0	+	+	0	+
AML300023	2	2	0.86	+	+	–	+	+	+	+
AML080017	2	2	0.57	+	–	0	.	+	+	+
AML030038	2	2	0.86	+	0	+	+	+	+	+
AML300024	2	2	0.86	+	0	+	+	+	+	+
AML370006	2	2	0.57	+	+	0	+	–	0	+
AML030040	2	1	0.57	0	–	+	+	0	+	–
AML100009	2	2	0.86	+	+	–	+	+	+	+
AML230031	2	2	0.86	+	–	+	+	+	+	+

Displayed are representative sequences of 10 patients from the >5-year survivor patients (B) as well as from 5-year nonsurvivor patients (C) of database DJ/REPP32.B14. Patients are classified according to the highest number of positional coincidences between the patient and disease classification masks (A). Parameter values below the 25% percentile are represented by (–), values between the 25% and 75% percentiles by (0), values above the 75% percentile by (+) and missing values by (.).

The results emphasize the potential of data pattern classification for individualized disease course predictions in AML. The predictions represent dynamic predictions because they are therapy dependant. A dynamic prediction may shift within hours from danger to unproblematic under preventive therapy in nonmalignant diseases, such as during sepsis or shock development in intensive care patients (10,11). The early recognition of danger may avoid or reduce irreversible tissue destruction or multiorgan failure.

Pretherapeutic nonsurvival prediction in the relatively therapy-resistant AML may favor the indication for therapy intensification or early stem cell transplantation. It may also result in the search for early therapeutic interference points in case of premalignant myelodysplastic syndromes.

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LITERATURE CITED

1. Löwenberg B, Downing JR, Burnett A. Acute myeloid leukemia. N Engl J Med 1999;341:1051–1062.
2. Byrd JC, Mrozek K, Dodge RK, Carroll AJ, Edwards CG, Arthur DC,

Pettenati MJ, Patil SR, Rao KW, Watson MS, Koduru PRK, Moore JO, Stone RM, Mayer RJ, Feldman EJ, Davey FR, Schiffer CA, Larson RA, Bloomfield CD. Pretreatment cytogenetic abnormalities are predictive of induction success, cumulative incidence of relapse, and overall survival in adult patients with de novo acute myeloid leukemia: results from cancer and leukemia group B (CALGB 8461). Blood 2002;100:4325–4336.

3. Frohling S, Schlenk RF, Breitruck J, Benner A, Kreitmeier S, Tobis K, Dohner H, Dohner K. Prognostic significance of activating FLT3 mutations in younger adults (16 to 60 years) with acute myeloid leukemia and normal cytogenetics: A study of the AML study group Ulm. Blood 2002;100:4372–4380.
4. Bernstein ID. CD33 as a target for selective ablation of acute myeloid leukemia. Clin Lymphoma 2002;2(Suppl 1):9–11.
5. Di Bona E, Sartori R, Zambello R, Guercini N, Madeo D, Rodeghiero F. Prognostic significance of CD56 antigen expression in acute myeloid leukemia. Haematologica 2002;87:250–256.
6. Raspadori D, Damiani D, Michieli M, Stocchi R, Gentili S, Gozzetti A, Masolini P, Michelutti A, Geromin A, Fanin R, Lauria F. CD56 and PGP expression in acute myeloid leukemia: impact on clinical outcome. Haematologica 2002;87:1135–1140.
7. Valet G. Predictive medicine by cytomics: potential and challenges. J Biol Regul Homeost Agents 2002;16:164–167.
8. Repp R, Schaekel U, Helm G, Thiede C, Soucek S, Pascheberg U, Wandt H, Aulitzky W, Bodenstein H, Kuse R, Link H, Ehninger G, Gramatzki M, AML-SHG study group. Immunophenotyping is an independent factor for risk stratification in AML. Cytometry Part B 2003;53B:11–19.
9. Bartsch R, Arland M, Lange S, Kahl C, Valet G, Höffkes H-G. Lymphoma discrimination by computerized triple matrix analysis of list mode data from three-color flow cytometric immunophenotypes of bone marrow aspirates. Cytometry 2000;41:9–18.
10. Valet G, Kahle H, Otto F, Bräutigam E, Kestens L. Prediction and precise diagnosis of diseases by data pattern analysis in multiparameter flow cytometry: melanoma, juvenile asthma and human immunodeficiency virus infection. In: Darzynkiewicz Z, Crissmann HA, Robinson JP, editors. Cytometry. 3rd edition. San Diego: Academic Press; 2001; Meth Cell Biol 64:487–508.
11. Tarnok A, Bocsi J, Pipek M, Osmancik P, Valet G, Schneider P, Hambsch J. Preoperative prediction of postoperative edema and effusion in pediatric cardiac surgery by altered antigen expression patterns on granulocytes and monocytes. Cytometry (CCC) 2001;46:247–253.
12. Stone RM. The difficult problem of acute myeloid leukemia in the older adult. CA-A Cancer J Clinicians 2002;52:363–371.
13. Kern W, Schoch C, Haferlach T, Braess J, Unterhalt M, Wörmann B, Büchner T, Hiddemann W. Multivariate analysis of prognostic factors in patients with refractory and relapsed acute myeloid leukemia undergoing sequential high-dose cytosine arabinoside and mitoxantrone (S-HAM) salvage therapy: relevance of cytogenetic abnormalities. Leukemia 2000;14:226–231.