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Significance in acute myeloid leukemia (AML) of bcl-2 protein expression

Sir,

The bcl-2 gene has been characterized as an important programmed cell death suppressor gene. The pathogenesis of several neoplastic disorders, including AML, has been related to bcl-2 overexpression.[1] Phenotypic and genotypic markers in AML, including bcl-2 oncoprotein, were recently evaluated with differing results regarding prognostic significance.[2,3]

We studied the bcl-2 protein in 30 patients diagnosed with *de novo* AML in our institution in the last 2 years. Their age, sex, FAB categories, proportion of leukemic cells expressing cytoplasmic bcl-2 protein, CD34 and lymphoid (Ly+) antigens, karyotypic abnormalities, PCR evaluation of bcl-2 gene rearrangement and clinical evolution are shown in Table 1. Cytoplasmic bcl-2 protein expression in leukemic cells was evaluated by immunocytochemistry only (Streptavidin-Biotin-Alkaline phosphatase method). PCR analysis to detect the usual bcl-2 gene rearrangement (MBR and mcr regions of chromosome 18) was performed according to published methods.

All patients were arbitrarily classified in 4 groups according to the percentage of leukemic cells expressing the bcl-2 protein: group I, no bcl-2 expression and group II, III and IV had a positive expression (Table 1). CD34 antigen was found in 86% of the patients from group I and in 40% of the bcl-2 positive groups. Ly+ antigens were observed in 57% of the patients from group I and in 35% of the patients with bcl-2 expression. Both B and T antigens were seen in group I, but only T antigens were present in groups II-IV. Cytogenetic abnormalities were not specific for each group of patients, and bcl-2 gene rearrangement was not found in any of the 8 patients studied.

After diagnosis, 26 patients received induction chemotherapy with 1 or 2 standard courses of chemotherapy: 22 patients achieved first complete remission, followed by consolidation therapy in 20 of these cases. Four refractory patients expressed the bcl-2 protein and 4 out of 5 who relapsed showed an increased proportion of bcl-2 + leukemic cells.

The bcl-2 expression was observed in different FAB categories of AML and showed no specific relationship to CD34 or Ly+ antigen expression; these findings differ from other recently published results.[1,2,4] The negative findings in our patients for the usual chromosomal or molecular bcl-2 gene rearrangements support the assumption that the dysregulation of bcl-2 gene and bcl-2 protein expression in AML and other neoplasias follow a mechanism which is different than the usual t(14;18) found in follicular lymphoma.[1,5] All patients refractory to our standard initial treatment were bcl-2 positive cases, furthermore, in 4 patients, bcl-2 expression increased at relapse. Thus, although further trials and longer follow-up are necessary, the bcl-2 cytoplasmic expression in our AML patients is apparently related to poor initial chemotherapy responses, as others have suggested.[1,2,4]

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Table 1. Clinical characteristics and evolution of 30 AML patients according to bcl-2 expression.

Group	*Sex/Age*	*FAB*	*CD34 %*	*Ly+ %*	*karyotype*	*PCR bcl-2*	*Evolution/bcl-2 %*
Group 1	M 25	M2	45	Neg	NM	NA	Relapse 30%
(bcl-2 negative)	F 71	M2	28	Neg	NM	NA	NT
	F 80	M2	13	CD2 23%	NM	NA	NT
	M 27	M2	50	CD7 82%	NM	NA	CR
	F 46	M4	54	CD20 40% CD2 61%	NM	NA	Exitus in CR
	M 14	M2	90	CD19 62%	NN	NA	CR
	F 62	M2	0	Neg	46 XX del(9q)	NA	CR
Group 2	M 69	M5b	0	Neg	NM	NA	NT
(bcl-2 < 20%)	F 69	M1	20	CD7 10%	NM	NA	Refractory
	F 58	M6	0	Neg	46 XX del(5q)	NA	Refractory
	M 56	M3	NA	Neg	NM	NA	CR
	F 47	M4	0	Neg	NN	NA	Relapse / 65%
	F 63	M1	70	Neg	49 XX +2, +3, +10	NA	CR
	F 46	M2	0	Neg	NN	NA	CR
Group 3	M 45	M0	0	Neg	46 XY -21, +mar	NA	Exitus in CR
(bcl-2 20-59%)	F 64	M2	40	CD2 15%	NN	NA	Relapse / 40%
	M 17	M1	0	CD3 25% CD7 70%	45 XY -10	NA	Relapse / 100%
	M 36	M1	71	CD2 44% CD3 18%	NN	NA	CR
	M 49	M1	0	Neg	47 XY +9	NA	CR
	M 39	M1	72	CD7 63%	47 XY +21	NA	CR
	M 31	M2	63	CD7 43%	46 XY del(3p)	NA	Refractory
Group 4	M 16	M1	0	Neg	NN	NA	Refractory
(bcl-2 60%)	F 17	M1	52	CD3 24%	47 XX +8	Neg	CR
	M 52	M2	0	Neg	47 XX +8	Neg	Relapse / NA
	M 40	M3	0	Neg	46 XY t(15 ;17)	Neg	CR
	F 80	M4	49	CD5 34%	NM	Neg	NT
	F 69	M3(V)	0	Neg	46 XX t(15 ;17)	Neg	CR
	F 27	M2	31	Neg	46 XX del(17q)	Neg	Exitus in CR
	F 45	M2	0	Neg	NM	Neg	CR
	M 37	M3	0	Neg	46 XY t(15;17)	Neg	CR

M: male, F: female, NA: not available, NN: normal, NM: no metaphases, Ly+: proportion of leukemic cells expressing lymphoid markers, Neg: negative, NT: not treated, CR: complete remission.

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Median versus mean lifetime survival in the analysis of survival data

Sir,

In survival studies, the median has traditionally been used to quantify the survival pattern of a particular patient population through a single parameter. Medians, however, demonstrate a well-known limitation because they are not influenced by the shape of the survival curve after 50% of residual survival has been reached. In other terms, medians are unaffected by the size of the *right tail* of the survival curve and are insensitive to the presence (or absence) of a small proportion of long-term survivors. In recent reports,[1-7] a new methodology of *lifetime* survival analysis has been proposed wherein the survival curves are evaluated by quantifying the area under the survival curve from time zero to infinity (AUC). According to this lifetime methodology, the portion of the curve from zero time to the last time point of the follow-up is estimated by direct numerical integration, whereas the right tail of the curve (from the last timepoint of the follow-up to infinity) is determined by an extrapolation based on the Gompertz model (Figure 1). If the AUC is normalized to a single patient, its value provides an estimate of mean lifetime survival (MLS).

Regardless of its useful applications in the analysis of cost-effectiveness,[1-7] MLS can be advantageous because it is sensitive to the shape of the curve after achievement of 50% residual survival, and therefore takes account of the presence (or absence) of a small proportion of long-term survivors.

Initial experience has been gained in the use of MLS. The literature has already reported MLS values of: 16.7 yrs in patients with node-positive breast cancer given adjuvant CMF chemotherapy vs. 13.2 yrs in patients given no adjuvant chemotherapy,[2] 2.9 yrs in patients with advanced ovarian cancer given first-line treatment with paclitaxel+cisplatin vs. 2.5 yrs in patients given cyclophosphamide+cisplatin;[3] 15.4 yrs in patients with colorectal cancer treated with adjuvant intraportal chemotherapy vs. 13.2 yrs in patients given no adjuvant chemotherapy;[4] 18.4 yrs in patients with relapsed chemosensitive non-Hodgkin's lymphoma treated with autologous bone marrow transplantation vs. 4.4 yrs in patients treated with salvage chemotherapy;[5] 9.6 yrs in patients with high-risk resected cutaneous melanoma treated with adjuvant interferon vs. 6.6 yrs in patients given no adjuvant therapy.[6]

Because simple theoretical considerations underscore an advantage of MLS for its sensitivity to the shape of the final portion of the survival curve, MLS can presently be regarded as a useful parameter for interpreting survival data. The Gompertz model for extrapolation of survival curves implicitly incorporates a prediction of the life expectancy of the patients. Other attempts have recently been made to include life expectancy data into survival curves.[8] The method of Vaidya and Mittra[8] seems to be more suitable for disease conditions characterized by a substantial chance of cure, whereas the Gompertz model is better suited for diseases with a low rate of cure. When the survival data derive from a particularly long follow-up, both models can be appropriate.

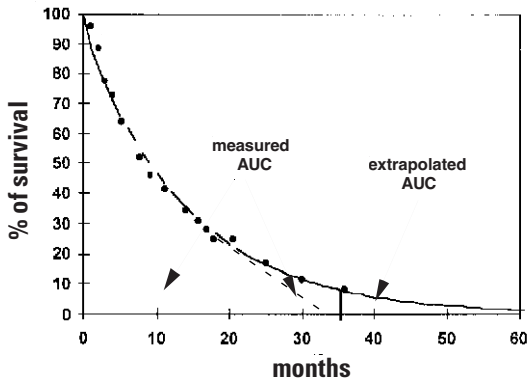

Figure 1. A least-squares fit of the trial's survival percentages (solid circles) to the Gompertz function allows to determine the whole survival curve as a mathematical function from time zero to infinity (solid line). The area under the survival curve can be split into a first component (measured AUC), which corresponds to the follow-up duration of the clinical trial, and a second component (extrapolated AUC), which corresponds to a survival prediction after the period over which the experimental data were available. If total AUC is normalized to 100 patients, MLS can be calculated as total AUC/100. The dotted line shows the time-course of another survival curve with no long-term survivors in which the median remains unchanged but both AUC and MLS are markedly reduced.

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