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Acute Leukemias

Bone marrow aspirate on the 14th day of induction treatment as a prognostic tool in *de novo* adult acute myeloid leukemia

VINCENZO LISO, FRANCESCO ALBANO, DOMENICO PASTORE, PAOLA CARLUCCIO, GIUSEPPE MELE, MARIELLA LAMACCHIA, ANNA MESTICE, GIORGINA SPECCHIA
Department of Hematology, University of Bari, Bari, Italy

ABSTRACT

Background and Objectives. **In adult acute myeloid leukemia (AML), a variety of clinical and biological parameters have been examined for their potential value in predicting treatment response. Early response to induction therapy could be an important prognostic factor in this disease.**

Design and Methods. **We studied the relationship between reduced blasts in bone marrow aspirate on the 14th day (BMA14th) of induction chemotherapy and treatment outcome in 198 adult AML patients of whom 124 were < 60 years old (group A) and 74 ≥ 60 years old (group B). Receiver operating characteristic curve analysis was used to assess the prognostic performance of BMA14th. Using the percentages of blasts of ≤ 22% and ≤ 15% as criteria for predicting treatment outcome gave the highest accuracy in terms of sensitivity and specificity in groups A and B, respectively.**

Results. **In group A, of 97 patients with a BMA14th ≤ 22%, 77 (79%) achieved complete remission (CR), whereas of 27 patients with a BMA14th >22%, 22 (81%) were non-responders (NR) ($p < 0.0001$). The test sensitivity and specificity were 93.9% and 71.4%, respectively. In group B, of 27 patients with a BMA14th ≤ 15%, 18 (67%) achieved CR, whereas of 47 patients with a BMA14th >15%, 38 (81%) were NR ($p = 0.0001$). The test sensitivity and specificity were 66.7% and 80.9%, respectively.**

Interpretation and Conclusions. **Our data suggest that BMA14th may be a predictive test for CR, helping to identify NR patients early in their disease. Further studies are needed to establish the practical implications of the results of our study.**
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Key words: acute myeloid leukemia; prognostic factors; complete remission

Correspondence: Vincenzo Liso, M.D., Department of Hematology, University of Bari, Policlinico, piazza G. Cesare 11, 70124 Bari, Italy. Phone: international +39.080.5478711 – Fax: international +39.080.5428978 – E-mail: emadhba@cimedoc.uniba.it

Advances in chemotherapy and supportive care have significantly improved the prognosis of patients with AML, but a fair number of them fail to respond to induction therapy and many patients who achieve complete remission (CR) relapse within two years.[1-3] Poor outcome of adult acute myeloid leukemia (AML) has been associated with advanced age, increased CD34 cell surface marker expression, increased LDH level and specific cytogenetic abnormalities, e.g. deletion on chromosomes 5 and 7 and a complex karyotype.[4-11] Identification of specific clinical and biological features of AML could provide information about the chance of CR in patients with newly diagnosed AML, while early identification of patients with resistant disease might indicate the need for a different chemotherapy approach. Previous studies demonstrated that in patients with AML the mean percentage of leukemic cells in the bone marrow on day 6 was significantly higher in patients who failed to respond than in those who obtained CR.[12,13] In childhood acute lymphoblastic leukemia, the lack of clearance of blasts from the bone marrow aspirates after 1 or 2 weeks of remission induction chemotherapy[14-19] or the persistence of circulating blasts after 1 week of multiagent chemotherapy[20] seems to identify a subset of high-risk patients with a higher rate of treatment induction failure. In adult AML we found that patients failing to respond to first line treatment had higher values for the marrow leukemic index (MLI).[21] This was found to be a highly independent reproducible prognostic tool for identifying patients likely to respond to 2nd line treatment. In this study we assessed the prognostic value of bone marrow aspirate on the 14th day (BMA14th) in 198 adult patients with *de novo* previously untreated AML. The BMA14th was evaluated together with biological parameters such as CD34 and CD7 surface marker expression, LDH serum level and leukocyte count at onset of disease.

Design and Methods

Patients

We analyzed a series of 198 patients (99 males and 99 females, aged 15-80 years, median 54 years) with *de novo* AML observed at our Institution between January 1992 and December 1998 (Table 1). According to the FAB classification[22] 10 patients had M0, 15 M1, 93 M2, 34 M4, 32 M5, 12 M6 and 2 M7. Patients with M3 were not included in this study. One hundred and twenty-four patients were aged ≤ 60 years (group A) (median 46, range 15-59) and 74 were ≥ 60 years old (group B) (median 67, range 60-80). The patients were treated according to GIMEMA-EORTC protocols: forty-three patients aged < 60 years were treated with the AML8A and AML8B, 81 with the AML10; seventy-four patients ≥ 60 years old were treated with the AML13 protocol. They were subdivided according to whether they had achieved CR or had resistant leukemia (we excluded patients who died early, before the induction treatment evaluation).

Induction treatment

AML8A-B. Daunorubicin 45 mg/m^2 on days 1,2 and 3. Arabinoside cytosine (Ara-C) 200 mg/m^2 on days 1-7, as continuous IV infusion.

AML10. Twenty-five patients were treated with the ICE protocol: idarubicin; 10 mg/m^2 days 1, 3 and 5; cytarabine: 25 mg/m^2 IV bolus followed immediately by 100 mg/m^2 given as a continuous infusion daily for 10 days; etoposide: 100 mg/m^2 in 0.9% saline daily by IV infusion over 1 hour on days 1-5. Twenty-seven patients were treated with the MICE protocol (idarubicin is replaced by mitoxantrone): mitoxantrone, 12 mg/m^2 IV infusion days 1, 3 and 5. Twenty-nine patients were treated with DCE: (idarubicin relapsed by daunorubicin); daunorubicin, 50 mg/m^2 days 1, 3, and 5.

AML13. Mitoxantrone: 7 mg/m^2/day on days 1,3 and 5 as 30 minute IV infusions. Etoposide: 100 mg/m^2 on days 1,2, and 3 as 1 hour IV Ara-c: 100 mg/m^2 on days 1-7, as continuous IV infusion.

Immunophenotypic analysis

Leukemic cell analysis was performed on bone marrow and peripheral blood cells by standard direct or indirect immunofluorescence methods using monoclonal antibodies (MoAbs) directed against CD2, CD3, CD4, CD5, CD7, CD8, CD10, CD11b, CD13, CD14, CD15, CD19, CD33, CD34, CD45, CD56, CD117, HLA-DR and C219 (Becton Dickinson). Flow cytometric analysis was performed on a FACScan flow cytometer (Becton Dickinson Immunocytometry System, Mountain View, CA, USA). A sample was considered antigen-positive if > 20% of the leukemic cells reacted with a particular MoAb.

Table 1. Clinical and biological features of 198 AML patients < 60 yrs (group A) and ≥ 60 yrs (group B). *Bone marrow aspirate performed on the 14th day after the start of induction treatment.

Group A (AML patients < 60 years)

	CR	*NR*	*p*
N. patients	82	42	
Sex			
Male	41	22	
Female	22	20	ns
Age	45 (16-59)	48 (15-59)	ns
FAB			
M0	1	4	
M1	7	5	
M2	37	20	
M4	18	4	
M5	18	7	
M6	0	1	
M7	1	1	ns
WBC	28.0 (0.6-268.0)	19.7 (1.0-215.0)	ns
LDH	728 (180-2519)	601 (202-2735)	ns
CD34 +/-	27/32	21/11	ns
CD7 +/-	9/47	13/18	0.01
*BMA14th %	4 (0-50)	42 (2-96)	< 0.0001
*BMA14th ≤ 22%	74 (90%)	12 (29%)	< 0.0001

Group B (AML patients ≥ 60 years)

	CR	*NR*	*p*
N. patients	27	47	
Sex			
Male	9	27	
Female	18	20	ns
Age	66 (60-77)	67 (60-80)	ns
FAB			
M0	2	3	
M1	1	2	
M2	16	20	
M4	2	10	
M5	3	4	
M6	3	8	ns
WBC	7.8 (1.1-450.1)	14.8 (0.5-253.0)	ns
LDH	923 (258-2242)	747 (285-5244)	ns
CD34 +/-	14/13	33/11	ns
CD7 +/-	6/18	5/37	ns
*BMA14th %	8 (0 - 55)	36 (0 - 90)	< 0.0001
*BMA14th ≤15%	18 (67%)	9 (19%)	0.0001

Bone marrow aspirate

Bone marrow was aspirated prior to the start of chemotherapy and on the 14th day of induction treatment. Aspirate differential counts were performed using May-Grünwald-Giemsa stained slides. The diagnosis and classification of AML in each case was reviewed by three of the authors and was based on established and updated FAB

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criteria.[22] In our hands, bone marrow aspirate allows a clearer morphologic definition of the cells than histology does, especially for evaluating small blast cells. The cellularity of the bone marrow aspirate was estimated microscopically as the number of nucleated cells, and was classified as low, intermediate and high, as previously reported.[21] Day 14 status was defined by the percentage of identifiable blast cells expressed as a total of the nucleated cells present. The differences between observers were averaged by taking the mean (median of differences was 2.5%, 2-4% range). Slides were classified as adequate or inadequate for assessment and the latter were rejected.

Response to treatment

Complete remission and relapse were defined according to the National Cancer Institute criteria.[23]

Statistical evaluation

A two-tailed Fisher's exact test was used to compare categories; the Kolgomorov-Smirnov test was used to assess whether the data were sampled from a population with a Gaussian distribution. Student's t-test or the Mann-Whitney test was performed to compare means. Receiver operating characteristic (ROC) curve analysis was used to assess the prognostic performance of BMA14th.[24-26] True-positive (TP) patients achieved CR and true-negative (TN) patients did not respond to treatment. False-positive (FP) patients were non-responders (NR) despite their test results falling within the criterion value. False-negative (FN) patients achieved CR but their test results were higher than the criterion value. The ability of BMA14th to predict CR was determined using the following formula: sensitivity = [(TP/TP+FN)]; specificity = [(TN/TN+FP)] and the criterion value with the highest accuracy (minimum false negative and false positive results). A useful alternative method for evaluating test efficiency is the likelihood ratio. The positive likelihood ratio (LR^+) is defined as sensitivity/(1-specificity). When this ratio exceeds 1, the odds favoring positive diagnosis increase, while as it approaches 1, the test is less accurate. The negative likelihood ratio (LR^-) is defined as (1-sensitivity)/specificity. There is perfect separation of the values of the two groups (positive and negative groups) when the area under the ROC curve (AUC) is equal to 1; the area is equal to 0.5 when there is no difference between the two distributions. The 95% confidence interval for the area was used to test the hypothesis that the theoretical area is 0.5. The binary logistic regression model was used to analyze the statistically significant parameters found at univariate analysis. Only p values < 0.05 were considered to be statistically significant.

Results

No difference was found in terms of response to treatment between the groups receiving different chemotherapy regimens.

In group A, 82 patients (66%) achieved CR, whereas 42 patients (34%) were NR. The median BMA14th value was 4% (range 0-50%) in CR patients and 42% (range 2-96%) in NR patients ($p < 0.0001$) (Table 1). The criterion value of ≤ 22% had the highest accuracy in terms of sensitivity and specificity (Figure 1). Of the 97 patients who had a BMA14th ≤ 22%, 77 (79%) achieved CR; conversely, of the 27 patients who had a BMA14th >22%, 22 (81%) were NR ($p < 0.0001$). The sensitivity and the specificity of the test were 93.9% and 71.4%, respectively; the AUC was 0.86 (95%C.I.= 0.795- 0.922) and LR^+ and LR^- were 3.29 and 0.09, respectively (Table 2). CD7 espression was higher in the NR than in the CR patients ($p = 0.01$). In the logistic regression model only BMA14th confirmed its prognostic role in terms of response to treatment ($p < 0.0001$). The other biological parameters considered in this study, such as LDH , WBC count, and CD34 surface marker expression, were not correlated with treatment outcome (Table 1).

In group B, 27 patients (36%) achieved CR, whereas 47 patients (64%) were NR. The median value of the BMA14th was 8% (range 0-55%) in CR patients and 36% (range 0-90 %) in NR patients ($p < 0.0001$). The criterion value of ≤ 15% had the highest accuracy in terms of sen-

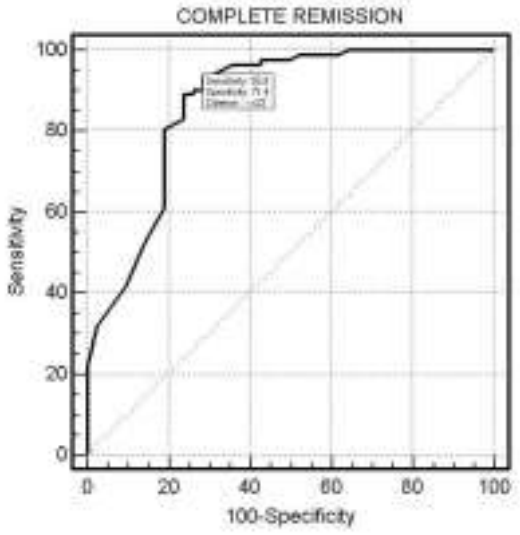

Figure 1. Receiver operating characteristic (ROC) curve analysis in 124 AML patients < 60 years (group A).

Table 2. ROC (receiver operating characteristic) curve results of 124 AML patients < 60 years old (group A) and 74 AML patients ≥ 60 years old (group B).

	Group A	*Group B*
Sensitivity	93.9%	66.7%
Specificity	71.4%	80.9%
Positive likelihood ratio	3.29	3.41
Negative likelihood ratio	0.09	0.4
AUC	0.86	0.78
95% C.I.	0.795-0.922	0.675-0.873

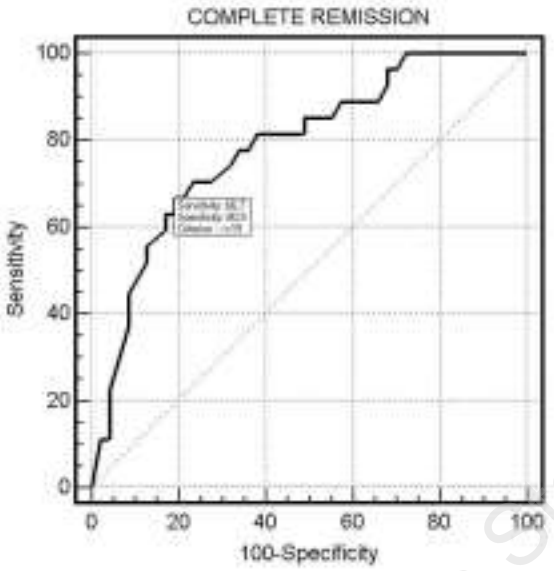

Figure 2. Receiver Operating Characteristic (ROC) curve analysis in 74 AML patients ≥ 60 years (group B).

sitivity and specificity (Figure 2). Of the 27 patients who had a BMA14th ≤ 15%, 18 (67%) achieved CR, whereas of the 47 patients who had a BMA14th >15%, 38 (81%) were NR (p = 0.0001). The sensitivity and the specificity of the test were 66.7% and 80.9%, respectively; the AUC was 0.78 (95% C.I. = 0.675-0.873) and LR$^+$ and LR$^-$ were 3.41 and 0.4, respectively (Table 2). CD34 expression was more frequently associated with the NR than the CR group, although this was not statistically significant. No differences in LDH value, CD7 expression and WBC count at diagnosis were found between the NR and CR groups.

Discussion

To date there is no parameter predicting early outcome of treatment in AML patients before the evaluation of response to induction chemotherapy. Many attempts to find an index characterizing a subgroup of AML patients at high risk of remission induction failure have been reported.[27-30] The rapidity of disappearance of blasts from the bone marrow after the start of induction treatment has been studied; in fact, some studies have evaluated the response to induction therapy by assessing the degree of residual leukemic infiltration in the bone marrow following 6 or 14 days of chemotherapy. Roberts *et al.*[28] described that in 39 patients bone marrow biopsy performed on day 6 of induction chemotherapy identified only 50% of the patients with resistant disease. In patients with AML aged less than 60 years, Browman *et al.*[12] described a model based on evaluation of bone marrow biopsy cellularity or abnormal cells on aspirate obtained on day 6 of induction therapy; patients with >30% bone marrow biopsy cellularity or >10% blast cells on the aspirate underwent *augmentation* of remission induction chemotherapy obtaining the same CR rate as the *non-augmented* group, suggesting that more aggressive therapy modifies the prognostic significance of residual leukemia in the bone marrow on day 6. In a previous experience the GIMEMA group demonstrated that the marrow leukemic index was predictive of the outcome of treatment in patients affected by AML who failed to respond to a single course of first line induction therapy.[21] It is now clear that the overall outcome of elderly patients with AML is much worse than that of younger patients with the same disease. In fact, AML in older patients is frequently characterized by resistance to treatment due to host and leukemia-related factors: the presence of co-morbid disease, such as diabetes, vascular insufficiency and renal impairment frequently compromises the host's tolerance to aggressive chemotherapy, while the metabolism of chemotherapeutic drugs may be delayed due to an age-related decline in excretory function, thus resulting in exposure to higher drug levels and greater toxicity.[31,32] Moreover, recent studies have led to a better understanding of the inherent biological differences between AML in the elderly and the same disease in younger patients, in terms of expression of drug-resistance genes, abnormal expression of the MSH2 protein involved in DNA mismatch repair and genome protection, abnormalities of chromosome 5 and/or 7.[7,32-35] These biological disease features, together with host-related factors, are associated with a relatively poor response to chemotherapy presumably affecting the clearance of blasts from blood and bone marrow. Because of these biological and age-related features, in our analysis we distinguished between younger (group A < 60 years) and elderly patients (group B ≥ 60 years), in order to investigate the most accurate criterion of bone marrow aspirate cellularity on the 14th day of induction treatment.

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In our series of 198 adult patients with *de novo* AML, treated with standard induction chemotherapy, the BMA14th evaluation was able to predict treatment outcome efficiently. BMA14th may help to distinguish between patients likely to achieve CR or to fail to benefit from standard chemotherapy. BMA14th ≤ 22% and ≤ 15% had high sensitivity and specificity in group A and group B, respectively. Furthermore, bone marrow aspirate cellularity on the 14th day of induction therapy is a simpler method than bone marrow biopsy for identifying patients who are likely to achieve CR. Notably, in our series there was a subset of high-risk patients who could not be identified either by the initial biological features or the BMA14th value. Although detection of early clearance of initial leukemic cells does not identify all patients who will achieve CR, this approach is simple and easily performed. Our data suggest that the prognostic significance of the BMA14th could help to identify patients with resistant disease who might benefit from alternative therapeutic strategies. In our opinion, BMA14th may be a useful parameter for guiding the decision to restart chemotherapy as soon as possible in risk cases. The results of our study should be the basis for further analysis examining the possibility of evaluating BMA14th in patients who relapse during salvage treatment.

The use of BMA14th, in addition to other parameters such as cytogenetic evaluation, may be a predictive test for CR, helping to identify NR patients early in their clinical course.

Contributions and Acknowledgments

VL and GS were responsible for the conception and design of the study and data interpretation. FA and AM performed the statistical analyses and interpretation of data. DP, PC, GM, ML were involved in the clinical management of the patients.

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Disclosures

Conflict of interest: none.

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Manuscript processing

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Potential implications for clinical practice

- The use of BMA14th criteria, in addition to other parameters, may be useful for predicting complete remission.

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