Clinical features and outcomes of 134 Brazilians with acute promyelocytic leukemia who received ATRA and anthracyclines

We report an increased incidence of high relapse risk features in 157 APL Brazilian patients. Out of 134 patients treated with ATRA and anthracyclines, only 91 (67.9%) achieved remission because 43 (32%) died during induction. The death rate during consolidation was 10.5%. Bleeding complications were the most frequent cause of failure (21.6%).

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There is sufficient evidence in literature to support the belief that all-trans retinoic acid (ATRA) and concomitant anthracycline-based chemotherapy should be the treatment of choice for newly diagnosed acute promyelocytic leukemia (APL).[1,2] In Brazil, APL accounts for more than 20% of acute myelogenous leukemias (AMLs),[3] a higher incidence than that reported in developed countries. Nevertheless, despite the fact that anthracyclines and ATRA are widely available, the results with standard treatment are not known.

We retrospectively analyzed medical chart data of 157 APL patients treated from January 2003 to March 2006 at 12 Brazilian institutions. The diagnosis was based on detection of the t(15;17) chromosomal translocation by cytogenetic analysis or of PML/RARα rearrangement by RT-PCR analysis. Laboratory diagnosis of disseminated intravascular coagulation (DIC) was based on changes in activated partial thromboplastin time, prothrombin time, fibrinogen degradation products (FDPs), and/or D-dimers. Central nervous system, pulmonary, or gastrointestinal hemorrhages were considered a severe bleeding. Patients were classified according to the risk of relapse on the basis of WBC and platelet counts (PLT) at diagnosis: low risk, WBC ≤ 10×10^9/L and PLT > 40×10^9/L; intermediate risk, WBC ≤ 10×10^9/L and PLT ≤ 40×10^9/L; and high risk, WBC > 10×10^9/L.[4]

Survival analysis was carried out for 134 patients who received anthracyclines (daunorubicin or idarubicin) plus ATRA in induction, ATRA and anthracyclines (daunorubicin, idarubicin, mitoxantrone or pharmarubicin) with or without citarabine in consolidation, and long term low dose chemotherapy in maintenance as proposed by Fenaux *et al*.[5] Blood bank support was available in all the centers, however, not all of them adopted prophylactic transfusions based on fibrinogen concentrations. Early mortality was defined as death within 14 days of diagnosis. Survival rates were estimated by the Kaplan-Meier method, and compared using the log-rank test. Differences among the risk groups regarding frequencies of bleeding and DIC at diagnosis, and mortality rates were compared using the χ^2 test. APL patients represented 28.2% of AML cases in the analyzed population. This is consistent with the previously reported higher frequency in patients with *Latino* ancestry.[6,7] The median WBC counts (Table 1) was higher than those reported in literature.[4,5] Consequently, the frequency of high-risk patients was significantly higher than that reported by PETHEMA and GIMEMA[4] (36.9 vs 22.6%, p=0.009). Although the time taken to reach specialized care was not accessed, studies on other hematological malignances suggest that this factor may be associated with the frequency of high tumor burden. The incidence of severe bleeding did not differ from that previously reported[8] but was associated with high mortality. DIC, severe bleeding and early mortality were more frequent in the high-risk group (p=0.015, p=0.001 and p<0.001 respectively) (Table 1). PML-RARα isoform distribution did not differ from that described in *nonlatino* populations.[9] This is in contrast to the reported excess of the BCR1 subtype in Mexican Mestizos.[10]

Among 134 patients available for survival analysis, 13.4% died within 5 days of diagnosis and 26.4% died within the first 14 days. This was mainly due to bleeding (66.6%). Induction and consolidation mortality were 32.0% and 10.5% respectively (Table 1). Three patients (2.2%) relapsed after consolidation and died. All patients alive after induction where in hematologic remission. The overall survival curves of all patients and of those who sur-

Table 1. Clinical and laboratory features and causes of mortality.

	Value	*p*
Age - mean (range), years	36 (5-79)	
Sex - n (%)		
Male	72 (45.8%)	
Female	85 (54.2%)	
WBC counts – median (range)×10^9/L	4.9 (0.3-403)	
Platelet counts – median (range)×10^9/L	24 (5-193)	
Risk assessment – n (%)		
Low risk	29 (18.5%)	
Medium risk	70 (44.6%)	
High risk	58 (36.9%)	
Severe bleeding at diagnosis - n (%)	27 (17.2%)	
Low risk *	1	<0.001
Medium risk*	7	
High risk *	19	
Laboratory evidence of DIC at diagnosis - n (%)	71 (45.2%)	0.012
Low risk*	12	
Medium risk*	24	
High risk *	35	
BCR subtype (n/total)†		
1	19/35	
2	2/35	
3	14/35	
Early mortality§ - n (%)	33 (26.4%)	
Low risk *	2	<0.001
Medium risk*	6	
High risk*	25	
Induction mortality§ - n (%)	43 (32.1%)	
Causes of death		
Bleeding	26 (60.5%)	
ATRA syndrome	4 (9.3%)	
Bleeding and ATRA syndrome	4 (9.3%)	
Bleeding and infection	2 (4.7%)	
Bleeding, infection and ATRA syndrome	3 (7.0%)	
Infection and ATRA syndrome	1 (2.3%)	
Unknown/other	3 (7.0%)	
Consolidation mortality§ - n (%)	14 (10.5%)	
Causes of death		
Bleeding	3 (21.4%)	
Infection	4 (28.6%)	
Bleeding and infection	2 (14.3%)	
Relapse	1 (7.1%)	
Unknown/other	2 (14.3%)	
Maintenance mortality§ - n (%)	3 (2.2%)	
Mean Survival – days (CI, 95%)		
Overall	706.7 (583.7-819.7)	
Induction mortality excluded	1045.5 (593.7-819.7)	
Low risk*	896.6 (747.0-1046.1	<0.001
Medium risk*	848.8 (678.6-1019.0)	
High risk*	319.6 (190.6-448.5)	

**Relapse risk groups; . §From 134 patients available for survival analysis; †Data from 35 patients was available for BCR subgroup analysis.*

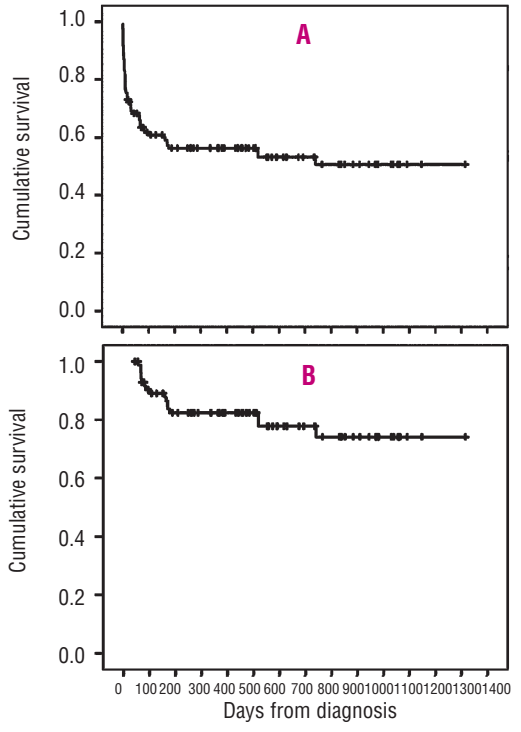

Figure 1. Overall survival of APL patients treated with ATRA in combination with anthracyclines in Brazil. A. Analysis of all patients. B. Analysis excluding patients who died during induction.

vived beyond induction are shown in Figures 1A and B respectively. The comparative analysis of these two curves reinforces the hypothesis that support during induction is the major issue to be addressed in developing countries. No significant differences were found between centers (data not shown). As high risk patients had a higher early mortality (Table 1), risk classification may identify patients who need a specific assessment, not only in consolidation, but also more intensive supportive care during induction.

Two important issues require particular attention. In the present study, no patient was excluded on the basis of age or performance status. This contrasts with published clinical trials and suggests that the prognosis of APL is not as favorable as is sometimes stated. Neither is the availability of drugs *per se* sufficient to reduce the gap in outcome between APL patients in developed and those in developing countries. Quicker diagnosis and better supportive care are required. With this aim, the International Consortium on Acute Promyelocytic Leukemia created a unified simplified treatment protocol and a support network offering online bi-weekly conferences with specialists, guidelines and monitoring of supportive care, centralized monitoring of treatment response by molecular biology methods, and an internet data base of patients from Brazil, Mexico and Jordan. We hope that this program will help change the disappointing results reported here.

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References

1. Avvisati G, Lo CF, Diverio D, Falda M, Ferrara F, Lazzarino M, et al. AIDA (all-trans retinoic acid + idarubicin) in newly diagnosed acute promyelocytic leukemia: a Gruppo Italiano Malattie Ematologiche Maligne dell'Adulto (GIMEMA) pilot study. Blood 1996;88:1390-8.
2. Sanz MA, Martin G, Gonzalez M, Leon A, Rayon C, Rivas C, et al. Risk-adapted treatment of acute promyelocytic leukemia with all-trans-retinoic acid and anthracycline monochemotherapy: a multicenter study by the PETHEMA group. Blood 2004;103:1237-43.
3. Onsten T, Girardi FM, Coelho GM, Lima Frey MC, Paskulin G. Cytogenetic and morphological findings in 166 patients with de novo acute myeloid leukemia in southern Brazil. Cancer Genet Cytogenet 2006;170:167-70.
4. Sanz MA, Lo CF, Martin G, Avvisati G, Rayon C, Barbui T, et al. Definition of relapse risk and role of nonanthracycline drugs for consolidation in patients with acute promyelocytic leukemia: a joint study of the PETHEMA and GIMEMA cooperative groups. Blood 2000;96:1247-53.
5. Fenaux P, Chastang C, Chevret S, Sanz M, Dombret H, Archimbaud E, et al. A randomized comparison of all transretinoic acid (ATRA) followed by chemotherapy and ATRA plus chemotherapy and the role of maintenance therapy in newly diagnosed acute promyelocytic leukemia. The European APL Group. Blood 1999;94:1192-200.
6. Douer D, Preston-Martin S, Chang E, Nichols PW, Watkins KJ, Levine AM. High frequency of acute promyelocytic leukemia among Latinos with acute myeloid leukemia. Blood 1996;87:308-13.
7. Sierra M, Alonso A, Odero MD, Gonzalez MB, Lahortiga I, Perez JJ, et al. Geographic differences in the incidence of cytogenetic abnormalities of acute myelogenous leukemia (AML) in Spain. Leuk Res 2006;30:943-8.
8. Visani G, Gugliotta L, Tosi P, Catani L, Vianelli N, Martinelli G, et al. All-trans retinoic acid significantly reduces the incidence of early hemorrhagic death during induction therapy of acute promyelocytic leukemia. Eur J Haematol 2000;64:139-44.
9. Douer D, Santillana S, Ramezani L, Samanez C, Slovak ML, Lee MS, et al. Acute promyelocytic leukaemia in patients originating in Latin America is associated with an increased frequency of the bcr1 subtype of the PML/RARα fusion gene. Br J Haematol 2003;122:563-70.
10. Ruiz-Arguelles GJ, Garces-Eisele J, Reyes-Nunez V, Gomez-Rangel JD, Ruiz-Delgado GJ. More on geographic hematology: the breakpoint cluster regions of the PML/RARα fusion gene in Mexican Mestizo patients with promyelocytic leukemia are different from those in Caucasians. Leuk Lymphoma 2004;45:1365-8.