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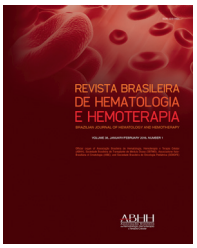

Original article

Molecular and hematologic relapses in adult patients with acute promyelocytic leukemia: a cohort study

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ABSTRACT

Objective: To evaluate factors predictive for relapse in a cohort of adult patients with acute promyelocytic leukemia monitored by molecular methods during consolidation and during at least one month of maintenance therapy.

Methods: The charts and laboratory data of 65 adult patients with acute promyelocytic leukemia treated according to the International Consortium on Acute Promyelocytic Leukemia 2006 protocol were reviewed. The identification of the *promyelocytic leukemia-retinoic acid receptor-alpha* gene rearrangement at diagnosis, post-induction, post-consolidation and during maintenance treatment was performed by qualitative and quantitative reverse transcription polymerase chain reaction.

Results: Eighty-nine patients were diagnosed with acute promyelocytic leukemia over a seven-year period and of these 65 were eligible for treatment with the protocol. Among the 45 patients who received consolidation and maintenance treatment, six (13%) relapsed, three of whom presented hematologic and three presented molecular relapse. The first relapses occurred at a median of 39 months. Relapsed patients were from all risk groups (low, intermediate and high) and both morphological types (M3 and M3variant) were found. Three of these patients are alive and in molecular remission after salvage treatment. There were no statistically significant differences regarding gender, age, risk group, morphology, promyelocytic leukemia breakpoint cluster region, use of all-trans retinoic acid, development of differentiation syndrome and number of days to complete remission between the patients who relapsed and those who did not.

Conclusion: Our results reinforce the importance of prolonged monitoring of acute promyelocytic leukemia patients using molecular methods to detect relapse early.

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Introduction

Once considered a leukemia with poor prognosis, currently by means of adequate treatment, acute promyelocytic leukemia (APL) is highly curable, with remission rates of 90% and disease-free survival at six years of over 80%.[1] Despite the increase in overall survival, cases of relapse still occur and need to be promptly identified, thus allowing pre-emptive treatment in the case of molecular relapses or re-induction in cases of hematologic relapse.[2]

The International Consortium on Acute Promyelocytic Leukemia (IC-APL 2006) aimed to deploy a network of National and International centers to improve diagnosis, treatment, monitoring of treatment response and support therapy and as a consequence the survival of patients with APL in developing countries. The treatment was based on the APL 2005 protocol of the Programa Espanhola de Hematologia (PETHEMA) group, adapted to the reality of the participating countries (Brazil, Mexico, Chile, Uruguay) with the substitution of the anthracycline idarubicin for daunorubicin which is more affordable and is widely used in the treatment of other leukemias.[3] Of the eight Brazilian centers participating in the IC-APL, the center of this study is the only representative of the northeastern region and included almost one third of the patients of the study.

The recently published results of the IC-APL[3] demonstrated an improvement in early mortality rates and overall survival compared with historical controls.[4] In the present study, a cohort of patients diagnosed with APL was evaluated for risk factors associated with relapse.

Methods

Patients

This study retrospectively analyzed 89 adult patients diagnosed with APL between January 2007 and August 2014 at the Hospital of the Fundação de Hematologia e Hemoterapia de Pernambuco (Hemope), Recife, Brazil. Clinical and laboratory data were obtained from the patients' charts. The project was approved by the Research Ethics Committee of the institution (#028/2006) and was conducted after informed consent was obtained from the patients.

Diagnosis and monitoring

The diagnosis was established by clinical, cytomorphological, immunophenotypic and molecular criteria.[5] The identification of the *promyelocytic leukemia-retinoic acid receptor-alpha* (*PML-RARα*) gene rearrangement was performed by reverse transcription polymerase chain reaction (nested RT-PCR and/or RT-qPCR) according to the international BIOMED-1 and BIOMED-2 protocols.[6,7] Samples for RT-qPCR were sent to the reference laboratory of the IC-APL study in the Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FMRP-USP).

Molecular tests were performed using bone marrow (BM) samples obtained at initial diagnosis, post-induction, post-consolidation (after the third course of consolidation) and during maintenance. Standard monitoring recommended tests every three and six months, respectively, during maintenance and after treatment for up to two years.

Definitions

Complete hematologic remission (CR) and relapse were defined using conventional criteria.[8] Hematologic relapse was diagnosed based on the presence of >20% blasts or abnormal promyelocytes in the bone marrow any time after hematologic remission. Molecular remission (MR) was defined as a negative RT-PCR result of bone marrow cells after the third and last cycle of consolidation.[9] Molecular persistence was defined as PCR positivity in two consecutive BM samples collected within a minimal interval of 15 days after the end of consolidation therapy. Molecular relapse was defined as the reappearance of the *PML-RARα*-specific band in two consecutive BM samples collected at an interval of 15 days at any time after consolidation therapy.[3,10] Arbitrarily, early relapse was defined as that occurring within two years after proven CR and late relapse beyond this period.[11] Differentiation syndrome (DS) was defined according to standard criteria.[12,13]

Treatment

The standard treatment protocol used was the IC-APL 2006 with patients being categorized according to the risk of relapse as described elsewhere.[3,9,14,15] The treatment options of the relapsed cases included re-induction with all-trans retinoic acid (ATRA), chemotherapy and arsenic trioxide (ATO) followed by stem cell transplantation (SCT) whenever possible.[2,16–18]

Statistical analysis

Statistical analysis was performed using the Stata 12.0 software. The *t*-test was used to compare the groups regarding age, days to CR, and months of follow up. Fisher's exact test was used for categorical variables (gender, risk of relapse, morphology and type of transcript). Relative risk (RR) was calculated with a 95% confidence interval (95% CI). *p*-Values <0.05 were considered statistically significant.

Results

Eighty-nine patients were diagnosed with APL during the period and of these, 65 were eligible for treatment using the IC-APL 2006 protocol. The median age at initial diagnosis of the relapsed patients was 37.5 years (range: 24–46 years). Hematologic remission was achieved with a median of 32 days (range: 27–56 days).

As the main purpose of this study was to evaluate factors predictive for relapse, analysis was restricted to the 45 patients who achieved remission and who were monitored during consolidation and maintenance. Therefore, 20 out of 65 patients were excluded because they died during

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