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Original article

Clinical and biological prognostic factors in relapsed acute myeloid leukemia patients☆

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ABSTRACT

Background and objective: Acute myeloid leukemia (AML) is the most frequent type of acute leukemia in adults. Despite recent advances in the characterization of pathogenesis of AML, the cure rates are under 40%, being leukemia relapse the most common cause of treatment failure. Leukemia relapse occurs due to clonal evolution or clonal escape. In this study, we aimed to analyze the clinical and biological factors influencing outcomes in patients with AML relapse.
Patients and methods: We included a total of 75 AML patients who experienced leukemia relapse after achieving complete remission. We performed complete immunophenotyping and conventional karyotyping in bone marrow aspirates obtained at diagnosis and at leukemia relapse.
Results: Overall survival (OS) of the series was 3.7 ± 2.3%, leukemia progression being the most common cause of death. Patients relapsing before 12 months and those with adverse cytogenetic-molecular risk had statistically significant worse outcomes. A percentage of 52.5 of patients showed phenotypic changes and 50% cytogenetic changes at relapse. We did not find significant clinical factors predicting clonal evolution. The presence of clonal evolution at relapse did not have a significant impact on outcome.
Conclusions: Patients with relapsed AML have a dismal prognosis, especially those with early relapse and adverse cytogenetic-molecular risk. Clonal evolution with phenotypic and cytogenetic changes occurred in half of the patients without predictive clinical factors or impact on outcome.

Factores pronósticos clínico-biológicos en pacientes con leucemia aguda mieloblástica en recaída

Palabras clave:
Leucemia aguda mieloblástica
Citometría de flujo
Recaída
Enfermedad mínima residual

RESUMEN

Fundamentos y objetivo: La leucemia aguda mieloblástica (LAM) constituye la leucemia más frecuente en adultos. A pesar de los avances en el conocimiento de su patogenia, las tasas de curación no superan el 40%, siendo la recaída de la enfermedad la causa más frecuente de fallo de tratamiento. La recaída ocurre por fenómenos de evolución clonal. En este estudio analizamos los factores pronósticos clínicos y biológicos en pacientes adultos con LAM en recaída.
Pacientes y métodos: Analizamos un total de 75 pacientes que presentaron recaída leucémica tras haber alcanzado la remisión completa. Se realizó un estudio inmunofenotípico mediante citometría de flujo y estudio citogenético mediante cariotipo convencional en muestras de médula ósea obtenidas en el momento del diagnóstico y de la recaída.
Resultados: La supervivencia global (SG) de la serie fue del 3,7% ± 2,3, siendo la principal causa de muerte la progresión leucémica (83,3%). Los pacientes con recaídas precoces –antes de 12 meses– y aquellos con riesgo citogenético-molecular adverso presentaron SG significativamente inferiores. En el momento de la recaída el 52,5% de los pacientes mostraron cambios fenotípicos, y el 50%, cambios citogenéticos, sin observarse factores clínicos predictivos de dicha evolución clonal. La evolución clonal fenotípica o citogenética no mostró ningún impacto significativo en la SG.

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Conclusiones: Los pacientes con recaída de LAM presentan un pronóstico infausto, especialmente aquellos con recidiva precoz y riesgo citogenético-molecular adverso. La evolución clonal fenotípica y/o citogenética ocurre en la mitad de los casos sin factores clínicos predictivos ni impacto pronóstico.

Introduction

Acute myelogenous leukemia (AML) is the most common acute leukemia in adults, with an incidence rate of 5–8 cases per 100,000 inhabitants per year and median age at diagnosis of 64–67, with an increasing incidence by age.[1] AML is biologically heterogeneous, with genetic alterations acquired sequentially in a myeloid precursor that cause blockage of normal maturation and uncontrolled proliferation. According to data from conventional and molecular cytogenetics, there are groups of good, intermediate and poor prognosis.[2,3]

AML treatment with curative intent requires intensive chemotherapy, which is only applicable to patients with generally good health condition. Despite obtaining a complete remission (CR) in 60–80% of patients with the classical scheme of cytarabine and idarubicin, current cure rates do not exceed 30–40%, even when including patients who undergo haematopoietic stem cell transplantation (HSCT) procedures. The main cause of treatment failure is leukemic relapse, which is due either to the persistence of a small number of leukemic stem cells that have been refractory to treatment, or because of the emergence of new leukemia cells with new genetic characteristics and phenotypic, which is defined as clonal evolution.[4,5] Once relapse occurs, the therapeutic options are limited and survival is very short.[6]

The aim of this study is to analyze the prognostic clinical characteristics of patients who have had an AML relapse and analyze the prognostic impact of biological behaviour (cytogenetic and phenotypic) of clonal evolution.

Patients and methods

Patients

The initial retrospective study population included a total of 416 patients consecutively diagnosed with AML (excluding subtype M3: promyelocytic) in our centre between January 1999 and May 2014. 217 of these 416 patients received intensive chemotherapy according to the Spanish Therapeutics Programme in Haematology current diagnosis protocols, 76% obtained CR. Of these, 75 (47%) patients had marrow leukemia relapse, constituting the study population.

The characteristics of the series are listed in Table 1; the median age was 59 years (1–76) and 48% of the population was older than 60. Of the total patients, 59 (78.7%) were diagnosed *de novo* with AML and the remaining 16 patients had leukemias secondary to other diseases.

According to international criteria by Cheson et al.[2] and the *European LeukemiaNet*[3] consensus, CR is defined as the presence of less than 5% of blasts in the bone marrow and more than 1000 neutrophils/mm^3 and 100,000 platelets/mm^3 in the peripheral blood without transfusion dependence, and no extramedullary disease. A marrow relapse is understood to be any recurrence of the disease, the presence of more than 5% blasts in bone marrow, the recurrence of blasts in peripheral blood, or development of extramedullary disease after achieving CR.

Samples

Obtaining samples of bone marrow at the time of diagnosis and relapse was through aspiration in the sternum or the iliac crest, obtaining 2–5 ml tubes with ethylenediaminetetraacetic (EDTA) or lithium heparin. The diagnosis of AML was performed with cytomorphology and cytochemistry data according to French-American-British criteria, and with genetic data according to 2008 World Health Organization criteria.

Table 1
Clinical characteristics of patients suffering from relapsed acute myelogenous leukemia at diagnosis.

Clinical characteristics at diagnosis (n = 75)	
Variables	n (%)
Sex (M/F)	39 (52)/36 (48)
Age; median 59 (1–76) years	
>60 years-old	36 (48)
AML de novo	59 (78.7)
Secondary AML	
MDS	9 (12)
MPS	2 (2.7)
Neoplasms	5 (6.7)
Karyotype	
Normal	39 (52)
del(7q)/−7	3 (4)
Complex	6 (8)
11q23	3 (4)
t(8;21)	5 (6.7)
tri(8)	2 (2.7)
t(3:3)	3 (4)
Others	9 (12)
NT	5 (6.7)
Molecular biology[a]	
NPM1−/FLT3−	25 (54.3)
NPM1+/FLT3−	9 (19.6)
FLT3+/NPM1−	6 (13)
FLT3+/NPM1+	5 (10.9)
Genetic and molecular risk	
Favourable prognosis	13 (17.3)
Intermediate prognosis	35 (46.7)
Unfavourable prognosis	26 (34.7)
Haematopoietic stem cell transplantation	
Auto	23 (30.7)
Allogeneic	20 (26.7)

AML: acute myelogenous leukemia; F: female; NT: not tested; MDS: myelodysplastic syndrome; MPS: myeloproliferative syndrome; M: male.
[a] Molecular biology was determined in patients with normal cytogenetics and NT patients.

Immunophenotypic analysis

For the immunophenotypic analysis 20 μl of bone marrow was incubated in EDTA for 10 min at room temperature with the following nonoclonales antibodies conjugated with fluorescein isothiocyanate, phycoerythrin, peridinin-chlorophyll protein complex or allophycocyanin: CD65, CD15, DR, CD7, CD2, CD14, CD19, CD117, CD56, CD13, CD11b, CD38, CD34, CD33. After incubation, the samples were lysed with ammonium chloride and resuspended in phosphate saline. Acquiring at least 30,000 leukemic events was performed in FACScalibur™ or FACSCanto™ II (Becton-Dickinson) flow cytometers. The analysis of phenotypic data comparing the diagnosis and relapse was performed using CellQuest™, FACSDiva™ and Infinicyt™ (Becton-Dickinson).[7]