Original Study

Evaluation of Parameters Related to the Probability of Leukemic Progression in Patients With Lower-Risk Myelodysplastic Syndrome

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Abstract

Several prognostic factors such as intermediate karyotype, presence of 5% to 9% bone marrow blasts, and platelet count <50 × 10e^9/L are related to the probability of leukemic progression in a cohort of patients with lower-risk myelodysplastic syndrome.

Background: The prognosis of patients with lower-risk myelodysplastic syndrome (LR-MDS) is very heterogeneous. In addition to survival estimates, identification of factors related to the probability of leukemic progression might help prognosis assessment. **Patients and Methods:** The present study is a retrospective analysis of 409 patients with primary LR-MDS. The probability of leukemic progression was estimated in the competing risk framework by the cumulative incidence method considering death without acute myeloid leukemia (AML) as a competing event. **Results:** Sixty-six patients (16.1%) progressed to AML. The following covariates influenced the probability of leukemic progression in a multivariate competing risk regression model: intermediate karyotype versus diploid or chromosome 5 deletion, 5% to 9% bone marrow blast percentage, platelet count <50 × 10e^9/L and age younger than 75 years. **Conclusion:** According to these, a predictive model is proposed, which categorizes patients with different probability of leukemic progression ($P < .001$). Validation of these results might help prognostic refinement of patients with LR-MDS.

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Introduction

Myelodysplastic syndromes (MDS) are defined as a group of clonal hematopoietic disorders characterized by dysplastic features in the bone marrow, ineffective hematopoiesis resulting in peripheral cytopenia, and eventual risk of progression to acute myeloid leukemia (AML).[1-3] The prevalence of MDS increases with age, affecting mainly older individuals with a median age at diagnosis of older than 70 years.[4] For treatment approaches, patients with the low and intermediate-1 categories according to the International Prognostic Scoring System (IPSS)[5] are defined as having lower-risk disease (LR-MDS). However, within this LR-MDS subgroup there is a wide clinical heterogeneity as shown by the prognostic refinement of the revised IPSS (IPSS-R),[6] together with the development of specific prognostic models for patients with lower risk disease.[7-10] These prognostic models consider age, severity of cytopenias, transfusion dependency, karyotype other than diploid or chromosome 5 deletion, and increase of bone marrow blasts for a better stratification in this set of patients. In addition to survival estimates, prognostic assessment for patients with LR-MDS must consider the eventual risk to leukemic progression. Classical prognostic scoring systems such as the IPSS[5] and the IPSS-R[6] have been used to evaluate the median time to AML evolution of patients with MDS. However, most patients categorized as low and intermediate-1 risk categories according to the IPSS or the very low, low, and intermediate categories according to the IPSS-R[6] died without evidence of evolution to AML, with infection, hemorrhage, and worsening of cytopenias being the most frequent causes of death.[11-14] With this

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rationale, this study was focused in the identification of factors related to the probability of leukemic progression considering death without AML as a competing event and to perform an analysis with the aim to predict the probability of progression to AML at a given time for an individual patient with LR-MDS.

Patients and Methods

Patients

A total of 437 patients with primary LR-MDS defined as having an IPSS score of low/intermediate-1 were retrospectively analyzed. This study included patients who received best supportive care with blood transfusion, erythropoietic stimulating agents, lenalidomide in case of LR-MDS with anemia and chromosome 5q deletion, and/or just observation if no symptomatic cytopenias. Patients who received hypomethylating agents or allogeneic stem cell transplantation during the follow-up period were excluded from analysis because those interventions could possibly affect survival.[15-17] The study was approved by the local ethics committee and was performed according with the Declaration of Helsinki.[18] Patient data were reviewed on the basis of electronic records at Hospital Universitario Virgen del Rocío (Seville, Spain) during the period from 1995 to 2017. Diagnosis of MDS was performed according to the French-American-British (FAB)[19] and the World Health Organization (WHO)[20] classifications. Prognostic stratification was according to IPSS,[5] IPSS-R,[6] and the M.D. Anderson Cancer Center lower-risk prognostic model.[7] From the initial cohort of 437 patients with lower-risk disease according to IPSS, subjects categorized as having high or very high risk categories after classification according to the IPSS-R or patients with poor and very poor cytogenetics according to Schanz et al[21] were removed from the analysis. Patients with nonproliferative chronic myelomonocytic leukemia with white blood cell count $<12 \times 10^9$/L were included because this group of patients was considered in the IPSS. The final cohort included 409 patients with LR-MDS.

Statistical Analysis

The probability of leukemic progression was analyzed and compared using the Gray test[22] in the framework of competing risk considering death without AML as a competing event. Multivariate analysis to identify predictive factors for leukemic progression was performed using the proportional subdistribution hazard regression model (Fine and Gray).[23] Clinical parameters that were shown to have a significant effect on leukemic progression in univariate analysis (those covariates with P values $<.1$) as well as those with clinical relevance were re-evaluated in the multivariate model. According to the stepwise approach, a final predictive model for the probability of leukemic progression was proposed. An assigned weight was applied to each parameter with prognostic effect for the probability of progression to AML. The diagnostic value of the scoring system was assessed using receiver-operating characteristic (ROC) curve analysis, using the Youden index to determine the optimal cutoff. Differences were considered to be statistically significant for 2-sided P values $<.05$. Confidence intervals (CIs) refer to 95% boundaries. The variables analyzed were age older than 75 years, transfusion dependency (defined as having al least 1 red blood cell transfusion every 8 weeks over a period of 4 months), hemoglobin <10 g/dL, platelet count $<50 \times 10e^9$/L, absolute neutrophil count, bone marrow blasts percentage (0-2% vs. 2%-4% vs. 5%-9%) cytogenetics (diploid and/or chromosome 5q deletion vs. other intermediate), and risk categories according to the M.D. Anderson Cancer Center lower-risk prognostic model.[5] Statistical analysis was computed with R version 3.0.2 software (R Core Team, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patient Characteristics

Median age at diagnosis of MDS was 74 (range, 31-93) years with 176 patients (43%) older than 75 years. Most frequent MDS subtypes and risk categories were refractory anemia and refractory cytopenia with multilineage dysplasia according to the FAB and WHO classifications, respectively, and intermediate-1 risk, low risk, and intermediate risk according to the IPSS, IPSS-R, and the M.D. Anderson Cancer Center lower-risk prognostic model, respectively. Other baseline demographic and clinical characteristics of the patients analyzed are shown in Table 1.

Survival and Leukemic Progression

After 103 months median follow-up (95% CI, 86-123), 298 patients (72.6%) had died. Median overall survival for the whole series was 41 months (95% CI, 34-47; see Supplemental Figure 1 in the online version), and 66 patients (16.1%) progressed to AML. Median time from diagnosis of MDS to documentation of leukemic progression was 31 months (range, 0.5-252 months). Significantly, the proportion of patients who died with leukemia (66 of 298 patients; 22.1%) was lower compared with patients who died of other etiologies (232 of 298; 77.8%). Cause of death was considered as MDS-related as stated in a previous report[10] and included those occurring after infectious complication, hemorrhage, progression to AML, and exacerbation of comorbidities related to worsening cytopenias. An MDS-related cause of death was recognized in 169 of 298 patients who had died at last follow-up (56.9%), not MDS-related in 79 of 298 patients (26.6%), and unknown in the remaining 50 patients (16.5%). In all patients with unknown cause of death, progression to AML could be excluded after evaluating the last available complete peripheral blood count and peripheral blood smear at last time of follow-up or death. Among MDS-related causes of death, exacerbation of comorbidities, mainly cardiovascular disease was the most frequent recorded, followed by infectious complications and progression to AML. At last-follow-up, 63 of 66 patients (95.2%) who developed AML have died, with a median survival of 1.9 months (95% CI, 0.1-3) from the date of progression to AML.

Parameters Related to the Probability of Leukemic Progression

Considering death without AML evolution as a competing risk, the following parameters influenced the probability of leukemic progression (Table 2 and Figure 1): age younger than 75 years ($P = .003$), platelet count $<50 \times 10e^9$/L ($P < .001$), bone marrow blasts percentage ($P < .001$), diploid karyotype or chromosome 5q deletion versus intermediate karyotype ($P < .001$), diploid karyotype versus 5q deletion versus intermediate karyotype ($P < .001$), and risk categories according to the M.D. Anderson Cancer Center lower-risk prognostic model ($P < .001$). Absolute neutrophil count reached marginal