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SCIENCE DIRECT®
Leukemia Research 29 (2005) 33–39
Leukemia Research
www.elsevier.com/locate/leukres

Clinical features of prognostic significance in myelodysplastic patients with normal karyotype at high risk of transformation

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Received 3 May 2004; accepted 10 May 2004

Available online 31 July 2004

Abstract

The International Prognostic Scoring System (IPSS) for myelodysplastic syndromes (MDS) has defined patients with a normal karyotype as a good risk cytogenetic subgroup, but nevertheless a fraction of these patients has a poor outcome similar to that of high risk patients. We retrospectively analysed our series of myelodysplastic patients with normal karyotype observed in a period of 11 years, with the aim of identifying clinical features of possible prognostic significance within this subgroup of patients. Multivariate analysis showed that among clinical scoring systems, the Bournemouth score appears the best prognostic indicator for risk of leukemic transformation, and platelet count $<100 \times 10^9/l^{-1}$, presence of haemorrhagic symptoms at time of diagnosis and morphologic FAB classification are the main prognostic factors for prediction of survival. In the absence of genetic abnormalities as detected by conventional cytogenetics or even the more sensitive molecular techniques in MDS, clinical variables could be of help in identifying patients with different prognosis, suitable for risk adapted therapeutic strategies.

Keywords: Myelodysplastic syndromes; Normal karyotype; Prognostic factors

1. Introduction

Myelodysplastic syndromes (MDS) are a group of heterogeneous clonal haematopoietic stem cell disorders characterized by dysfunctional haematopoiesis leading to bone marrow failure and high risk of progression to acute leukaemia.

Through multivariate analyses of large series of patients, several studies have shown that main prognostic factors in these disorders are percentage of bone marrow blasts, number and degree of cytopenias, age >65 years and presence of chromosomal abnormalities [1–3].

Based on these features, different scoring systems for prediction of outcome and risk of transformation to acute myeloid leukaemia (AML) have been created during the last two decades [4–9], the most used being the International Prognostic Scoring System (IPSS) that has defined four prognostic subgroups of MDS patients [10].

The IPSS evidences a normal karyotype at diagnosis as detected by conventional cytogenetics, in 40–65% of all MDS patients included in low risk group [10]. Nevertheless, this category of patients is very heterogeneous for the wide variability of clinical parameters and the outcome is often unpredictable.

In present study, we retrospectively evaluated 98 consecutive MDS patients with normal karyotype at CCA and analysed clinical features as detected at time of diagnosis, in order to establish their possible prognostic impact on survival and risk of evolution to acute leukaemia.

2. Patients and methods

2.1. Patients

Between January 1986 and December 1997, 98 patients were diagnosed at our Institution as having a myelodysplastic syndrome with a normal karyotype; this figure represents 58% of the whole MDS patients diagnosed over the same period of time. We included in the study only patients without

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0145-2126/$ – see front matter © 2004 Elsevier Ltd. All rights reserved.
doi:10.1016/j.leukres.2004.05.010

history of previous cytotoxic, chemo- or radiation exposure, and excluded patients with secondary or therapy-related MDS, according to WHO criteria [11]. Morphological examinations were performed using standard methods on peripheral blood and bone marrow Wright–Giemsa-stained films. Iron staining and non-specific esterase were used for the diagnosis of refractory anemia with ringed sideroblasts and chronic myelomonocytic leukaemia. Classification was performed according to FAB criteria [4]; we used FAB and not WHO revisited criteria because in the analysis were included patients with blasts >20% (RAEB-t), that in the past were considered MDS and not AML. Bone marrow aspirate was obtained in all cases at diagnosis and dysplastic features were recognized as previously indicated [4]. Cytogenetic analyses were conducted at the time of diagnosis by GTG banding technique on bone marrow cells obtained from short-term unstimolated cultures (24–48 h). Chromosomal abnormalities were identified by the International System for Human Cytogenetic Nomenclature (1995). At least 20 metaphases were analysed in all cases. Treatment of MDS phase was based on only supportive therapy in all patients. Only five patients received AML-like therapy after evolution.

2.2. Analysis of prognostic factors

The following characteristics at time of diagnosis were analysed to establish the association with survival and risk of transformation to acute leukaemia: age, sex, dysplastic lineage involvement, haemoglobin, white blood cell (WBC), platelet and neutrophils counts, percentage of blast cells in the bone marrow, presence of transfusional requirement, presence of hemorrhagic symptoms and/or infections.

The prognostic impacts of FAB classification and of three scoring systems were also evaluated. The first two systems, the Bournemouth and the Spanish scoring, are based only on clinical parameters while the International Prognostic Scoring Systems introduces also the karyotype [7,10,12].

According to this last system the stratification of patients in low, intermediate-1, intermediate-2 and high risk was only applied on the basis of clinical features, because for the normal karyotype the attributed score value is 0, i.e. considered as of “good prognosis”.

2.3. Statistical analysis

Univariate analysis for each prognostic variable on overall survival and time to disease evolution was estimated according to the Kaplan–Meier method. The terminal event was considered the death attributable to cancer or non-cancer causes. The statistical significance of the differences in survival distribution among the prognostic groups was evaluated by the log-rank test. The Cox proportional hazards model was applied to the multivariate survival analysis.

The prognostic variables for overall survival and time to leukemic evolution included: sex, age, FAB classification, Bournemouth score, Sanz score, IPSS score, lineages of bone marrow involvement, transfusions requirement, infectious and/or hemorrhagic complications, hemoglobin levels, WBC, neutrophils and platelets counts at diagnosis.

P-values <0.05 were regarded as statistically significant in two tailed tests. SPSS software (version 10.00, SPSS, Chicago) was used for statistical analysis [14–16].

3. Results

3.1. Clinical data

There were 59 males (60%) and 39 females (40%). Median age was 63.8 years (range 23–82.8). According to FAB classification there were 29 patients with RA (29%), 11 patients with RARS (11.2%), 26 patients with RAEB (26.5%), 8 patients with RAEB-t (8%) and 24 patients with CMML (24.4%).

In the peripheral blood, 47 patients had haemoglobin values <10 g/dl, 36 patients had neutrophil counts $<2.5 \times 10^9\,l^{-1}$, 31 patients had platelet counts $<100 \times 10^9\,l^{-1}$.

Morphological analysis revealed a bone marrow percentages of blasts <5% in 40 patients (41%), 5–10% in 38 patients (38.7%), 11–20% in 12 patients (12%) and >20% in 8 patients (8%). In 51 patients (52%) there was a trilinear bone marrow dysplasia.

Sixty patients (61.2%) required transfusional support; 44 patients (44.8%) had an infection and 13 patients (13.2%) presented one or more hemorrhagic events at the time of diagnosis.

Median survival of all 98 patients was 28.9 months. These data compared to a median survival of 21.7 months in the whole MDS population, observed in the same period.

By the end of follow-up (60 months), 41/98 patients (41.8%) have died, acute leukaemia being the main cause of death, with a transformation rate of 32% (13 patients); in 4 patients (9.8%) death was not related to the myelodysplastic disease and was mainly due to cardiovascular failure or second neoplasias.

3.2. Analysis of prognostic factors for survival and leukemic transformation

The results of the univariate analysis of prognostic factors for survival are summarized in Table 1.

Male sex ($P = 0.03$), age >65 years ($P = 0.03$), FAB category with high percentage of blasts ($P = 0.0002$) and presence of trilineage involvement ($P = 0.03$) were strictly associated with a shorter survival. At univariate analysis, also significant were haemorrhagic symptoms at diagnosis ($P = 0.002$), haemoglobin level <10 g/dl ($P = 0.03$),