Brief Communications

Prognostic impact of JAK2V617F mutation in myelodysplastic syndromes: A matched case control study

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A B S T R A C T

While in RARS-T, JAK2V617F mutation is common and associated with good prognosis, the clinical and prognostic impact of this mutation in other MDS is unknown. We collected data from 132 non-RARS-T MDS with known JAK2V617F mutation status. JAK2V617F mutation was significantly correlated with lower progression to AML (p < .0011) and better overall survival (OS, p = .011). OS difference persisted after matching on age, sex, IPSS and % marrow blast (p = .031). Thus, in MDS other than RARS-T, JAK2V617F mutation may be associated with favorable outcome.

1. Introduction

Acquired JAK2V617F somatic mutation is a hallmark of Philadelphia negative myeloproliferative neoplasm (MPN) [1,2]. In myelodysplastic syndromes (MDS), JAK2V617F mutation is seen in less than 5% of the cases [3]. Both 2001 and 2008 WHO classifications include among myelodysplastic/myeloproliferative (MDS/MPN) overlap syndromes [4] a provisional entity, refractory anemia with ringed sideroblasts associated with sustained thrombocytosis (RARS-T) that appears to have a relatively favorable prognosis [5] especially if JAK2V617F mutation, detected in about 60% of the cases, is present [3]. Apart from RARS-T, however, the impact of JAK2V617F mutation in MDS remains unknown [6–8].

We conducted a retrospective study of MDS patients with JAK2V617F mutation, after exclusion of RARS-T cases, where patients were compared with matched unmutated MDS without JAK2V617F mutation.

2. Materials/methods

2.1. Data collection

After approval by the Clermont-Ferrand University Hospital Ethics committee, a questionnaire was sent to all French centers of the Groupe Francophone des Myélodysplasies (GFM) and of the French Intergroup of Myeloproliferative neoplasms (FIM) to collect clinical, laboratory and follow up data in MDS patients with known JAK2V617F mutation status detected in blood by real-time polymerase chain reaction. We also obtained, from the GFM
registry of French MDS, data from patients where JAK2V617F mutation had been tested. In the absence of specific recommendations, JAK2V617F mutation in those patients had been assessed systematically at diagnosis in a few centers, or later in the disease course, mainly because of features with potential predictive value for JAK2V617F mutation, like thrombocytosis. Patients with chronic myelomonocytic leukemia, RARS-T and MDS following MPN were excluded [4].

2.2. Statistical analysis

Descriptive statistics were used to characterize the population on parameters collected at the time of diagnosis. Overall survival (OS) was defined from diagnosis to death or censored at latest contact with the patient. Time to acute myeloid leukemia (AML) progression was defined from diagnosis to date of AML. OS curves and OS estimates were determined using the Kaplan–Meier method. Patient characteristics and outcome according to JAK2V617F status were analyzed by univariate analysis using the chi-square test for qualitative analysis and Kruskal–Wallis test for quantitative analysis and log-rank test for OS comparison.

The primary endpoint of this retrospective analysis was to assess the impact of JAK2V617F mutation on MDS. In an attempt to reduce the effect of potential bias in this cohort, propensity score matching was used. This method allows balancing of all measured relevant variables between the 2 groups (JAK2V617F positive and negative).

Covariates included in the propensity-score model were sex, hemoglobin, WBC, ANC, platelet, IPSS, karyotype, marrow blasts and age known to be clinical relevant in MDS. OS analysis was performed with a Cox model adjusted with propensity score [9]. Statistical significance was considered below .05. Statistical analysis was performed using STATA 10.0 software (StataCorp, College Station, TX, USA).

3. Results

Data from 132 MDS patients with known JAK2V617F mutation status were collected in 19 centers of the FIM and GFM, including 37 JAK2V617F positive (JAK2+) and 95 JAK2V617F negative (JAK2 –) cases. Their main clinical and laboratory features are presented in Table 1. The JAK2V617F mutation burden was available in only 7 patients, showing a median level of 16% (range, 1–50%).

There were no significant differences between JAK2+ and JAK2 – cases in terms of age, gender, hemoglobin level, WHO 2008 classification, cytogenetic findings and IPSS. In JAK2+ patients, the white blood cells (WBC) count, absolute neutrophil count (ANC), platelet count and mean corpuscular volume (MCV)
were significantly higher, while the marrow blast percentage was significantly lower than in JAK2− cases.

Treatments used (Table 1) were similar in both patient groups, especially with regards to erythropoietic stimulating agents, chemotherapy and hypomethylating agents. Seventeen JAK2+ (45%) versus 36 (37.8%) JAK2− patients were red blood cell transfusion-dependent (p=.77).

Median follow up was 44 months (range 18–349) in JAK2+ and 69 months (range 32–185) in JAK2− patients (p=.95). OS was significantly longer in JAK2+ patients (median not reached) than in JAK2− patients (median 66 months) (p=.011) (Fig. 1). The estimated 5-year OS was 86% in JAK2+ patients versus 57% in JAK2− patients. The 10 year cumulative incidence of AML progression was significantly lower in JAK2+ (20%) than in JAK2− patients (47%) (p<.001).

When the analysis was matching with propensity score, OS was still significantly longer in JAK2+ patients (median not reached versus 73 months, p=.031) whereas JAK2 status had no significant prognostic value for OS in IPSS intermediate-2 and high patients (p=.18).

4. Discussion

In this series, which is to our knowledge the first to focus on MDS with JAK2V617F mutation other than RARS-T, we found JAK2+ cases to have higher WBC, ANC and platelet counts and fewer marrow blasts than JAK2− MDS, but no significant difference in cytogenetics and IPSS.