Original Study

Improved Survival of Calreticulin-Mutated Patients Compared With Janus Kinase 2 in Primary Myelofibrosis: A Meta-Analysis

Hampig Raphael Kourie,[1] Lieveke Ameye,[2] Marianne Paesmans,[2] Dominique Bron[1]

Abstract

Calreticulin (CALR) is a recently discovered mutation in patients with primary myelofibrosis (PMF). Six studies (Asian and non-Asian) met the inclusion criteria for the present meta-analysis, which has confirmed the role of the CALR mutation in the diagnosis of, and as a prognostic tool for, PMF. Our results suggest that patients with CALR mutation have better overall survival than patients with janus kinase 2 (JAK2) mutation in a non-Asian population.

Background: Next to janus kinase 2 (JAK2) and myeloproliferative leukemia protein, calreticulin (CALR) is a recently discovered mutation present in > 20% of patients diagnosed with primary myelofibrosis (PMF). **Materials and Methods:** Six studies published from December 2013 to December 2014 met the inclusion criteria for the present meta-analysis: 2 of an Asian and 4 of a non-Asian population. We assessed the biologic characteristics at diagnosis and investigated overall survival. The analyses were stratified by ethnic origin (Asian vs. non-Asian). **Results:** A total of 816 patients with the JAK2 mutation and 307 patients with the CALR mutation were included. The patients with the JAK2 mutation were older than those with the CALR mutation, and no statistically significant difference was noted in the gender distribution of the patients with PMF with the JAK2 versus CALR mutation. Patients with JAK2-mutated PMF had a higher white blood cell count, but no statistically significant evidence was found for a difference in the platelet count or hemoglobin level. No difference was found in thrombosis risk or acute leukemic transformation in those 2 populations. Major differences were found between the Asian and non-Asian populations. The difference in characteristics between JAK2 and CALR was larger in the Asian population than in the non-Asian population ($P = .007$). Also, in the non-Asian population, those with JAK2 mutation had lower platelet counts than the Asians ($P = .06$). In the non-Asian population, the patients diagnosed with JAK2-positive PMF had worse overall survival than the patients with CALR-positive PMF, with a combined hazard ratio of 2.43 (95% confidence interval, 1.83-3.22). **Conclusion:** The results of the present meta-analysis have confirmed the role of the CALR mutation in the diagnosis of, and as a prognostic tool for, PMF. Our results suggest that patients with the CALR mutation will have better overall survival than patients with the JAK2 mutation in a non-Asian population.

Clinical Lymphoma, Myeloma & Leukemia, Vol. ■, No. ■, ■-■
Keywords: Asian, Better prognosis, Comparison, Race, Survival

Introduction

Primary myelofibrosis (PMF) is 1 of 8 myeloproliferative neoplasms (MPNs), next to chronic myelogenous leukemia, chronic neutrophilic leukemia, chronic eosinophilic leukemia, mastocytosis, polycythemia vera, essential thrombocythemia (ET), PMF, and unclassifiable MPN.[1] PMF occurs mainly in elderly patients with a median age of 67 years.[2]

Patients diagnosed with PMF usually present with 1 of the following symptoms or signs: fatigue, splenomegaly, hepatomegaly, thrombosis, low-grade fever, and bone pain.[3] However, 15% to 30% of these patients will be asymptomatic at diagnosis.[3] According to the 2008 World Health Organization (WHO) classification, 3 major criteria and 2 of 4 minor criteria must be present to confirm the diagnosis of PMF. The 3 major criteria are typical bone marrow biopsy; not meeting the WHO criteria for polycythemia vera, PMF, chronic myelogenous leukemia, myelodysplastic syndrome, or other

[1]Hematology Department
[2]Data Centre, Jules Bordet Institute, Université Libre de Bruxelles, Brussels, Belgium

Submitted: Nov 10, 2015; Revised: Jan 20, 2016; Accepted: Jan 27, 2016

Address for correspondence: Hampig Raphael Kourie, MD, Hematology Department, Jules Bordet Institute, Université Libre de Bruxelles, Boulevard de Waterloo 121, Brussels 1000, Belgium
E-mail contact: hampig.kourie@hotmail.com

2152-2650/$ - see frontmatter
http://dx.doi.org/10.1016/j.clml.2016.01.009

myeloid neoplasms plus demonstration of JAK2V617F or another clonal marker; and no evidence of reactive marrow fibrosis. The 4 minor criteria are leukoerythroblastosis, increased serum lactate dehydrogenase level, anemia, and palpable splenomegaly.[1]

According to the WHO 2008 classification of MPNs, janus kinase 2 (JAK2) and myeloproliferative leukemia protein (MPL) mutations, which represent 60% and 5% of PMF cases, respectively, are considered one of the major diagnostic criteria for MPN. Recently, a new mutation, the calreticulin (CALR) mutation, was found in > 20% of patients with ET and PMF. Also, this mutation was mutually exclusive to the JAK2 and MPL mutations. These mutations have been found to be mutually exclusive, except for in some reported cases. CALR mutations are found on exon 9 of CALR and are of the insertion/deletion type. The gene encoding CALR is an endoplasmic reticulum calcium-binding chaperone and plays a role in ensuring the proper folding of newly formed proteins, maintaining the correct levels of calcium ions in this structure.[4]

The CALR mutation, present in > 20% of 2 different MPNs, will have a major effect on the diagnosis, classification, prognosis, and treatment of these diseases and will be considered a therapeutic or prognostic target in many trials. Knowledge of this mutation will also modify the WHO diagnosis criteria for ET and PMF.

Many studies since December 2013 have been published describing the different clinical and biologic characteristics of the CALR mutation in PMF compared with the JAK2 mutation.[5-10] However, these studies have presented some divergent findings. In the present meta-analysis of 6 studies, we present a complete survey with high evidence highlighting the biologic and clinical characteristics and survival of patients with PMF with the CALR mutation compared with the JAK2 mutation. Because 2 of the 6 studies included Asian populations and because of the specific mutational features of Asian populations in different malignancies, subgroup analyses were performed for the Asian and non-Asian ethnicities.

Materials and Methods

Search Strategy for Study Identification and Selection Criteria

Electronic searches of studies published from December 2013 to December 2014 were conducted using the PubMed database to identify those reporting the clinical and biologic characteristics of patients with PMF with the CALR mutation compared with the JAK2 mutation. We did not include studies of the MPL mutation because some of the published studies had not included the MPL mutation.

Only trials containing the CALR mutation in PMF were included. The search strategies used included key words and Boolean operators as follows: "primary myelofibrosis" and "calreticulin." This search was augmented by a manual search of the references of the relevant studies included in the literature review. Two different investigators performed the search (H.K., D.B.), and the abstracts were independently reviewed for possible inclusion.

Only descriptive studies comparing the clinical and biologic characteristics and outcomes of patients with PMF with the CALR mutation and those of patients with the JAK2 mutation were included in the present meta-analysis. The language of the eligible studies was restricted to English. The included studies were limited to adult patients with documented PMF according to the WHO classification.

Study Selection

The included studies were first selected individually by their titles by 2 of us (H.K., D.B.). Next, the abstracts of these studies were examined. Our searches yielded 32 study reports from the PubMed database. These selected reports were then evaluated by 2 of us (H.K., D.B.). Finally, 6 reports published from December 2013 to December 2014 were considered eligible by the 2 of us (H.K., D.B.) and were retrieved for data extraction. The information from some of the remaining studies were used in our introduction and discussion sections because they were review articles or original studies reporting other aspects of the relation between the CALR mutation and PMF.

Data Extraction and Study Appraisal

A total of 6 eligible studies were retrieved. A content assessment form was developed to extract relevant information by 2 of us (H.K., L.A.) in a standardized fashion. The information extracted for the 2 CALR and JAK2 mutation groups (2 mutually exclusive mutations) included the number of patients, distribution of the continuous variables of interest (age, hemoglobin level, white blood cell [WBC] count, and platelet count); distribution of the binary characteristics of interest (gender, acute leukemic transformation, thrombosis during follow-up [yes vs. no]), and overall survival data.

Statistical Analysis

The overall effect of the type of mutation (JAK2 vs. CALR) as a continuous variable was assessed by the difference in the mean values for the 2 groups of patients. The overall effect of JAK2 versus CALR as a binary variable was assessed using the combined odds ratio. Finally, the effect on overall survival was assessed by estimating the combined hazard ratio.

Using the summary data published in the eligible trials, individual differences in the mean values, individual odds ratios, and individual hazard ratios were estimated, together with their variances. The combined estimates of the effects were calculated through the use of fixed-effects models (for cases in which no heterogeneity could be detected) or random-effects models. Heterogeneity was tested using a χ^2 test. Statistically significant evidence was found for a difference between the JAK2- and CALR-mutated patients if the 95% confidence interval (CI) did not contain 0 in the case of an estimated mean difference or did not contain 1 in the case of an estimated odds ratio or a hazard ratio.

We performed an analysis of all 6 studies and analyses stratified by the ethnicity of the study population (Asian or non-Asian). The studies by Qiao et al[5] and Li et al[9] included an Asian population. We assessed whether an interaction effect was present with the population ethnicity (Asian vs. non-Asian). All analyses were performed using the Meta package in R, version 3.0.2.

Results

JAK2 and CALR Mutation Characteristics in PMF

The study results from the 6 studies were analyzed (n = 1381), including 816 patients (59%) with the JAK2 mutation, 307 patients (22%) with the CALR mutation, and 263 patients (19%) without either mutation. We assessed the differences in the patient characteristics between those with a JAK2 mutation and those with a