Original Study

Outcome Disparities in Caucasian and Non-Caucasian Patients With Myeloproliferative Neoplasms

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Abstract

This is a single institution retrospective experience examining the effect of race and ethnicity on disease phenotype in myeloproliferative neoplasms. We demonstrate racial disparities in the outcomes of myeloproliferative neoplasm, with Caucasian ethnicities being relatively protected against cardiovascular thrombosisis and hemorrhagic complications. African Americans are the ethnic sub-group at highest risk of hemorrhagic complications.

Background: The Philadelphia chromosome-negative myeloproliferative neoplasms (MPNs) are characterized by an increased risk of thrombotic and hemorrhagic complications. Large retrospective studies have demonstrated racial disparities in MPN outcomes and attributed this to differences in access to health care. Utilizing a single institution experience, we report outcomes in patients with polycythemia vera (PV), essential thrombocythemia (ET), and myelofibrosis in relation to ethno-racial background. **Patients and Methods:** A total of 127 Caucasian (56%) and non-Caucasian (44%) adult patients with MPNs consecutively treated at the University of Illinois between 1990 and 2012 were examined in this retrospective study. Relationships between ethno-racial background and vascular complications, and disease transformation were evaluated using multivariate logistic regression models. **Results:** Non-Caucasian PV patients had an increased risk of vascular complications including cardiovascular thrombosis and hemorrhagic events, while Caucasian patients with PV and ET had a higher risk of progression to myelofibrosis. In a Cox proportional hazard regression analysis, Caucasian race emerged as an independent prognostic factor protective against cardiovascular thrombosis in PV and ET patients (hazard ratio, 0.2; 95% confidence interval, 0.03-0.9; $P = .04$) while age > 60 years and prior thrombosis were significant risk factors in univariate analysis. Non-Caucasian race was also a significant risk factor in univariate analysis of hemorrhagic complications of PV and ET, and this was largely driven by African American ethnicity. **Conclusion:** This study shows for the first time that race can influence clinical outcomes in myeloproliferative neoplasms. Our findings highlight the need for greater representation of non-Caucasian patients in studies investigating vascular risk factors in MPNs.

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Introduction

Myeloproliferative neoplasms (MPNs) such as essential thrombocythemia (ET), polycythemia vera (PV), and primary myelofibrosis (PMF) are chronic hematologic malignancies characterized by the clonal proliferation of 1 or more myeloid lineages and the activation of JAK/STAT signaling.[1-3] Genomic analysis of the MPNs has revealed frequent mutational events in the JAK-STAT signaling pathway, including *JAK2*^{V617F} mutations in 95% of patients with PV and in 50% to 60% of patients with ET and PMF. Additional somatic mutations resulting in upregulated JAK-STAT

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signaling include mutations in the thrombopoietin receptor *MPL*, *JAK2* exon 12 mutations, and *LNK* mutations in $JAK2^{V617F}$-negative MPNs. Somatic calreticulin (*CALR*) mutations, observed in 70% to 80% of JAK2-*WT* ET and PMF patients,[4] were found to be mutually exclusive of *JAK2* and *MPL* mutations, suggesting a convergent mechanism of transformation, and transcriptional profiling confirms upregulation of JAK-STAT signaling activity.[5]

The incidence and outcome of MPNs across different races and ethnicities has not been extensively explored, although a recent study reported that Chinese patients are younger and have better outcomes compared with Caucasian patients.[6] In the United States, MPNs have similar incidence rates across different ethnicities.[7,8] A retrospective study from a nationwide registry (Surveillance, Epidemiology, and End Results Program [SEER]),[9] analyzing mainly elderly patients with MPN, demonstrated that the overall survival in MPNs is lower compared with matched non-MPN/non-cancer controls. Interestingly, despite the fact that non-Caucasian patients represented only 13% of ET, 11% of PV, and 10% of MF sub-groups, the SEER registry dataset reported an inferior outcome in black patients compared with white patients, which was attributed to differential access to health care.

To address this hypothesis, we analyzed a case series from a single urban health care institution that serves the health care needs of Caucasian and non-Caucasian patients. We retrospectively analyzed the outcomes of 127 consecutive patients with a diagnosis of a *bcr-abl*-negative MPN seen at the University of Illinois Hospital and Cancer Center between 1990 and 2012. We investigated differences in clinical presentation and outcomes of MPNs in Caucasians and non-Caucasians. Well-validated predictive models, such as the International Prognostic Score of thrombosis in ET, have identified cardiovascular risk factors and the JAK2V617F mutation as independent thrombotic risk factors, in addition to age $>$ 60 years and a history of prior thrombosis,[10] but race has not been addressed as a risk factor. There are also polymorphisms related to MPNs that differ by ethnicity. A polymorphism in the thrombopoietin receptor, Mpl Baltimore, is found exclusively in African Americans with a prevalence of approximately 8%, is associated with thrombocytosis, and has a different clinical phenotype than classic ET found in the general population.[11] This study is unique in examining the contribution of race to the risk of clinical complications in MPNs in a diverse population while controlling for health care access.

Methods

Study Patients

In this retrospective study, data from 128 patients between the ages of 18 and 80 years with the diagnosis of an MPN consecutively seen at the University of Illinois Hospital between 1990 and 2012 was collected by chart review. Of 128 patients, 1 was excluded from analysis owing to a diagnosis of familial polycythemia. All patients had self-reported documentation of race and ethnicity in the medical chart. The median duration of follow-up was 6 years (interquartile range [IQR], 3-11 years). Because no new data were collected, the study was exempt from patient consent requirements and was approved for conduct by the University of Illinois Institutional Review Board. This study had no external funding source.

Variables

The clinical, hematologic, and cytogenetic characteristics, type of MPN, incidence of thrombotic events, and the overall survival of these patients were investigated. The clinical data obtained at diagnosis included gender, age, ethnicity, occupation, white blood cell (WBC) count, hemoglobin, platelet count, erythropoietin level, and spleen size. Cytogenetic data was available on bone marrow biopsies of 76 (60%) patients, JAK2 mutational status was available on 105 patient (82%) of patients, and allele burden was reported in 27 patients (21%).

Patients were classified as polycythemia (PV), essential thrombocythemia (ET), and myelofibrosis (MF) based on World Health Organization 2008 diagnostic criteria.[12] The MF group included PMF as well as post-PV and post-ET MF. Patients in each disease group were stratified as Caucasian or non-Caucasian, where the latter included African Americans, Hispanics, or Asians. The following parameters were compared at diagnosis between Caucasian and non-Caucasian patients: age, gender, $JAK2^{V617F}$ mutation status, cytogenetic abnormalities, family history of MPNs, constitutional symptoms, WBC and platelet count, hemoglobin level, and spleen size. In patients with PV and ET, the grade of reticulin fibrosis at diagnosis, based on the Thiele semiquantitative scoring system,[13] which includes 4 grades of reticulin fibrosis (grades 0-3), was investigated as a marker for increased risk of progression to MF[14] and was available in 43% of cases. Data on personal or family history of a hematologic or other malignancy was also collected. The presence of vasomotor symptoms such as pruritis and headaches was documented, as well as any obstetric complications. Patients with MF were classified according to the Dynamic International Prognostic Scoring System.[15]

Clinical outcomes studied included thrombotic complications (defined as stroke, acute coronary syndrome, transient ischemic attack, pulmonary embolism, abdominal thrombosis, deep vein thrombosis, or peripheral arterial thrombosis). Thrombotic complications were classified as being present at diagnosis of an MPN or in the ensuing period following disease confirmation. The use of antiplatelet agents and anticoagulation was also recorded. Other outcomes studied were hemorrhagic events, progression or transformation of disease, secondary cancers, and overall survival. Treatments utilized in patients included phlebotomy and cytoreductive agents such as hydroxyurea or interferon, as well as allogeneic stem cell transplant for MF.

Statistical Analysis

The sample and subsamples, divided by disease sub-type, were described by ethnicity using frequency with percentage for categorical variables and median with IQR for continuous variables. To compare the difference between Caucasian and non-Caucasian patients' disease characteristics, the chi-squared test or the Fisher exact test was used for categorical variables, while the Wilcoxon rank-sum test was used for continuous variables. The Kaplan-Meier survival curve and the Peto-Peto test were conducted to describe the time-to-event outcomes. Also, we explored the effect of covariates of interest on 3 main outcomes (thrombosis during follow-up, progression to MF, and hemorrhagic events) by using logistic regressions and Cox proportional hazard models, whenever appropriate. We only focused on PV and ET disease sub-types for