Effect of Red Blood Cell Transfusion Dependence on the Natural History of Myeloproliferative Neoplasm-Associated Myelofibrosis

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Abstract

There is no consensus on the definition of red blood cell transfusion dependency for patients with myelofibrosis. We studied the effect of transfusion dependency according to 2 widely used definitions of transfusion dependence.

Background: There are 2 widely used criteria for red blood cell (RBC) transfusion dependence in persons with myeloproliferative neoplasm (MPN)-associated myelofibrosis: (1) the International Working Group-Myelofibrosis Research and Therapy (IWG-MRT) criteria (receipt of 2 U RBC in the preceding month); and (2) the Rand-Delphi definition (2 U RBC per month averaged over 3 months). We studied effect of these criteria on survival and risk of leukemic transformation in 259 subjects with MPN-associated myelofibrosis. **Patients and Methods:** On the basis of hemoglobin (Hb) and transfusion history, subjects were assigned to 1 of the 4 cohorts: (1) Hb $\geq$ 100 g/L (n = 136; 52%) and no RBC transfusions in the preceding 4 months; (2) Hb $<$ 100 g/L, and no RBC transfusions in the preceding 4 months (n = 56; 22%); (3) subjects who met IWG-MRT criteria, but not the Rand-Delphi criteria for RBC transfusion dependence (n = 34; 13%); and (4) subjects who met the Rand-Delphi criteria for RBC transfusion dependence (n = 33; 13%). **Results:** Three-year probability of survival among the 4 cohorts was 81% (95% confidence interval [CI], 71-87), 55% (95% CI, 36-71), 52% (95% CI, 31-69), and 47% (95% CI, 24-67), respectively (P = .0005). There was no significant difference in baseline characteristics or survival between cohorts 3 and 4 and they were combined for subsequent analyses. In multivariate analyses, subjects who met either definition of RBC transfusion dependence had significantly worse survival (hazard ratio, 2.61; 95% CI, 1.38-4.96; P = .01). **Conclusion:** RBC transfusion dependence is associated with worse survival irrespective of definition of transfusion dependence. No effect of anemia or RBC transfusion dependence on leukemic transformation was observed.

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Introduction

Primary myelofibrosis (PMF) is a disease characterized by clinical and laboratory findings that include megakaryocytic proliferation, bone marrow fibrosis, leukoerythroblastosis, palpable splenomegaly, inflammation-related symptoms, and often profound anemia. A disease phenotype similar to PMF is seen in later stages of the natural progression of polycythemia vera (PV) and essential thrombocythemia (ET), also known as post-PV myelofibrosis (PPV-MF) or post-ET myelofibrosis (PET-MF). In this article, these 3 entities have been collectively referred to as myeloproliferative neoplasm (MPN)-associated myelofibrosis.

There is controversy on how to define red blood cell (RBC) transfusion dependence in persons with MPN-associated myelofibrosis. There are 2 widely used criteria in this context: (1) the International Working Group-Myelofibrosis Research and Therapy (IWG-MRT) criteria defines RBC transfusion dependence as having received $\geq$ 2 U of RBC in the preceding month for an Hb $<$ 85 g/L that was not associated with clinically overt bleeding[1]; and (2) the Rand-Delphi criteria as having received $\geq$ 2 U of RBC per month over 3 months without any specification for the Hb level.[2] It is noteworthy that both of these definitions are based on expert opinions, and their comparative effect on the natural history of

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MPN-associated myelofibrosis has not been studied. We used the data from our center to determine whether the different criteria were associated with different outcomes.

Patients and Methods

This retrospective study was approved by the Cancer Registry and Data Access Committee and Research and Ethics Board of University Health Network. A total of 300 patients were identified from the institutional database, who were seen and treated in our program. Subsequently the diagnoses of all subjects were reviewed according to the World Health Organization (WHO) definition for PMF, and IWG-MRT criteria for PPV-MF and PET-MF.[3,4] A total of 41 subjects were excluded because they did not meet the WHO criteria, having already progressed to leukemic transformation at the time of referral, and bone marrow transplant performed at another institute before referral to our program. In addition, subjects who were only seen for a second opinion, and had no follow-up were excluded (Figure 1).

In total, 259 subjects were included in the analyses for this study. Risk stratification was done using the DIPSS at the time of confirmed diagnosis of PMF, PPV-MF, and PET-MF, or at the time of the first appointment at our center (if diagnosed elsewhere).[5] Comorbidities were calculated using the ACE-27.[6] Transfusion data on all subjects were collected for the 4 months before calculation of DIPSS. Data were collected on patient, disease, and treatment-related variables in a case report form specifically designed for this study.

Statistical Methods

Baseline characteristics on categorical variables were compared across groups using either the χ^2 test or Fisher exact test (as appropriate); the nonparametric Kruskall–Wallis test was used for numeric outcomes. Overall survival was calculated from the date of diagnosis or first presentation, if diagnosed elsewhere, to the date of death or last follow-up. Patients were censored if they were alive at last follow-up. Overall survival rates were calculated using the Kaplan–Meier estimate. Univariable and multivariable survival analyses were performed using the Cox proportional hazards model. Estimates of leukemic transformation over time were calculated using the cumulative incidence method (which accounts for competing risks) and compared using Gray's method. The competing risk analyses were produced using the cmprsk package in R version 3.1.1 (The R Foundation, Vienna, Austria). All other analyses were performed using SAS version 9.4 (SAS Institute Inc).

Figure 1 Study Cohort