To the editor:

White blood cell counts and thrombosis in polycythemia vera: a subanalysis of the CYTO-PV study

The pathogenesis of thrombosis in patients with polycythemia vera (PV) results from a complex interplay of patient- and disease-related variables. According to age and previous thrombosis, patients are traditionally stratified as "high risk" or "low risk." However, recently, novel disease-related determinants such as leukocyte (white blood cell [WBC]) levels and JAK2V617F mutational burden have been proposed as new contributing predictors of vascular events and are now under active investigation.[1] In the largest epidemiologic study (European Collaboration on Low-dose Aspirin), baseline leukocytosis emerged as an independent risk factor of arterial thrombosis,[2] and since then, no confirmatory data have been produced. The Italian randomized trial Cytoreductive Therapy in Polycythemia Vera (CYTO-PV) tested different intensities of cytoreductive therapy (phlebotomy and cytoreductive drugs) to prevent thrombotic events and showed that the arm maintained at hematocrit (HCT) target <45% had a significant 4 times lower rate of cardiovascular death and major thrombosis than did the arm with a HCT target of 45% to 50%. Analysis also showed that during the follow-up, patients in the high-HCT group had significantly higher WBC counts than did those in the low-HCT group.[3] As expected, the intensity of therapy (phlebotomy and hydroxyurea) was higher in the low-HCT than in high-HCT arm.[3] During the follow-up (median, 28.9 ± 10.9 months), the median HCT level in the low-HCT group was 44.4% compared with 47.5% in the high-HCT group. Fatal and nonfatal cardiovascular events were registered in 28 patients (7.7%), corresponding to an incidence rate of 3.4 per 100 person-years. Platelet levels did not differ in the 2 arms, whereas WBC count persisted at significantly higher levels in the high-HCT group than in the low-HCT group ($P < .001$). To discern the relative merits of more stringent HCT control from the role of a lower WBC count to reduce the cardiovascular events, we carried out a multivariable time-dependent analysis[4] by considering the level of WBC categorized into approximate quartiles and recorded in the last clinical visit before the thrombotic event. The study was approved by each Institutional Review Board. Results indicate that the risk of thrombosis was clearly increased in patients with WBC count $>7 \times 10^9$/L, becoming statistically significant when WBC count was $>11 \times 10^9$/L (Table 1).

Therefore, this analysis discerns the thrombogenic role of WBC from that of HCT and corroborates other prospective and retrospective studies in myeloproliferative neoplasms. In an analysis of 21 887 serial full blood counts in the prospective Primary Thrombocythemia 1 cohort, which included 776 essential thrombocythemia patients, one-third of them previously treated with cytoreductive drugs, with a median follow-up of 36 months (range, 2-87), the risk of thrombosis, both arterial and venous, was not significantly associated with platelet count or hemoglobin level, whereas there was a significant association between WBC count and risk of thrombosis ($P = .03$).[5] In another study of patients with World Health Organization–defined essential thrombocythemia, WBC $>11 \times 10^9$/L was associated with arterial thrombosis only (hazard ratio [HR], 1.7; 95% CI, 1.01-2.72; $P = .044$).[6] In primary myelofibrosis patients, the combination of a WBC count $>15 \times 10^9$/L and the presence of the JAK2V617F mutation was associated with an increased risk of arterial and venous thrombosis (HR, 3.13; 95% CI, 1.26-7.81).[7] Likewise, in early myelofibrosis, WBC count $>11.2 \times 10^9$/L was associated with an increased risk of arterial thrombosis (HR, 1.12; 95% CI, 1.00-1.25).[8]

In conclusion, WBC count is implicated in the process of thrombogenesis in PV and should be evaluated in the therapy response.

Table 1. Time-dependent multivariable analysis on the risk of major thrombosis in CYTO-PV study (N = 365)

WBC class ($\times 10^9$/L)	Events/pts (%)	Hazard ratio (95% CI), *P*
<7.0	4/100 (4.0)	1.00
7.0-8.4	4/84 (4.8)	1.58 (0.39-6.43), .52
8.5-11.0	8/88 (9.1)	2.69 (0.80-9.05), .11
≥11.0	12/93 (12.9)	3.90 (1.24-12.3), .02

Adjusted for age, gender, cardiovascular risk factors, previous thrombosis, and hematocrit levels.

CI, confidence interval; pts, patients.

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To the editor:

Improved outcomes associated with hematopoietic stem cell transplantation for patients with juvenile myelomonocytic leukemia

Allogeneic hematopoietic stem cell transplantation (HSCT) is the only reported cure for juvenile myelomonocytic leukemia (JMML).[1] However, HSCT outcomes remain suboptimal with only 50% event free survival at 5 years.[1,2] We conducted a retrospective study of 7 consecutive children who were diagnosed with JMML[3] and underwent an allogeneic HSCT at Children's Hospital Los Angeles between 2007 and 2014. Approval was obtained from the hospital's Institutional Review Board and the study was conducted in accordance with the Declaration of Helsinki.

Five patients (Table 1) received pre-HSCT therapy. The median patient age at HSCT was 2.6 years. All patients received backbone conditioning with BuMel; Bu 1 mg/kg dose every 6 hours IV on days −8 to −5 (with therapeutic drug monitoring to achieve overall concentration steady state [CSS] of 800-1000 ng/mL) and Mel 45 mg/m^2 per day IV on days −4 to −2. Two patients who received a 10/10 (HLA-A, B, C, DRB1, DQ) histocompatible related BM graft, were conditioned with BuMel only. One patient who received a 9/10 histocompatible related BM graft received BuMel and Flu 35 mg/m^2 per day IV on days −7 to −4; 1 patient who received a 9/10 MUD graft received BuMel and Alem 12 mg/m^2 IV on day −10 and 20 mg/m^2 on day −9. Methylprednisolone was administered at 2 mg/kg per day in divided doses during the Alem infusion. Three patients who received UCB grafts received BuMel and rATG 2.5 mg/kg per day IV on days −4 to −1. Methylprednisolone was administered at 2 mg/kg per day in divided doses during rATG infusion, and thereafter tapered over 6 weeks. All patients received tacrolimus for graft-versus-host disease (GVHD) prophylaxis. Methotrexate was also administered at 5 mg/m^2 dose on days 3, 6, and 11 to all patients, except UCB recipients. Standard supportive care guidelines were followed.[4]

The median (range) Bu CSS and area under the curve were 884 (560-1096) μg/L and 1293 (819-1601) μmol/L-minute, respectively. The median total nucleated cell count and CD34 cell dose were 4.2×10^8 cells per kg and 3.3×10^6 cells per kg, respectively. The median time to neutrophil engraftment (≥500/mm^3) and platelet engraftment (≥20 000/mm^3) was 20 and 36 days, respectively. Six (85.7%) patients achieved predominant (>95%) donor hematopoietic stem cell engraftment. One patient (#6) who received a UCB HSCT had autologous recovery at day +54; she received a related-haploidentical HSCT on day +105. At 100 days post–haploidentical HSCT, she is alive and in remission, with predominant donor chimerism. Another patient (#2) who received an MMSD HSCT developed grade 4 acute GVHD and later developed severe chronic GVHD, requiring bowel resection. This patient (#2) and patient #4 developed severe sinusoidal obstructive syndrome, which resolved with supportive care. At a median (range) length of follow-up of 25.3 (6-99.3) months, 100% of patients are alive and in clinical remission.

There is currently no standard conditioning regimen for children with JMML undergoing HSCT. In the largest clinical trial of patients with JMML given a uniform conditioning regimen, children received myeloablative doses of Bu (16-20 mg/kg orally over 4 days), cyclophosphamide (120 mg/kg over 2 days), and Mel (140 mg/m^2). The 5-year cumulative incidence of transplant-related mortality (TRM) and leukemia recurrence was 13% and 35%, respectively, and one-third of patients relapsed at a median time of 6 months post-HSCT.[1] Similar TRM and relapse rates were also recently reported among patients with JMML who received a myeloablative regimen of Bu (oral or IV), Mel (total dose 210 mg/m^2), and Flu (patients in our cohort received a total dose of Mel at 135 mg/m^2).[5]

It is possible that our target Bu CSS contributed to improved outcomes (decreased graft failure and TRM compared with prior reports with oral Bu and/or no therapeutic drug monitoring). It is also possible that administration of pre-HSCT chemotherapy to patients with more progressive disease may have contributed to improved outcomes. Among our patients, we did not observe any TRM. The BuMel backbone regimen was used to avoid total body irradiation (and its potential associated late effects especially among younger children who are often diagnosed with JMML). With no TRM and 100% of patients alive and in remission, we believe that BuMel may represent a successful conditioning strategy for patients receiving both conventional and alternative donor HSCT. A prospective clinical trial is warranted to confirm these promising findings.

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