

Effects of Hydroxyurea Therapy on Inflammatory Markers and Indices in Patients with BCR-ABL Negative Myeloproliferative Neoplasms

Öğuz Altunok¹, İstemi Serin², Osman Yokuş³

¹University of Health Sciences Türkiye, İstanbul Bakırköy Dr. Sadi Konuk Training and Research Hospital, Clinic of Oncology, İstanbul, Türkiye

²University of Health Sciences Türkiye, Başakşehir Çam and Sakura City Hospital, Clinic of Hematology, İstanbul, Türkiye

³University of Health Sciences Türkiye, İstanbul Training and Research Hospital, Clinic of Internal Medicine, İstanbul, Türkiye

ABSTRACT

Introduction: Chronic inflammation plays a central role in the pathogenesis and progression of Breakpoint Cluster Region- Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL)-negative myeloproliferative neoplasms (MPNs). Although hydroxyurea is widely used as a cytoreductive agent in this patient population, its impact on systemic inflammation remains unclear. This study aimed to evaluate the effect of hydroxyurea on inflammatory markers and indices in patients with MPNs.

Methods: In this retrospective study, 298 patients diagnosed with BCR-ABL-negative MPNs who were followed between 2010 and 2022 were analyzed. Patients were classified as polycythemia vera (PV), essential thrombocythemia (ET), primary myelofibrosis (PMF), or MPN-unclassifiable (MPN-u) according to the 2016 World Health Organization criteria. Laboratory parameters including leukocyte, neutrophil, lymphocyte, and platelet counts, C-reactive protein (CRP), and lactate dehydrogenase (LDH) were recorded at baseline and at months 3, 6, and 12. Inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR) and systemic immune-inflammation index (SII), were calculated. Statistical analyses were performed using non-parametric tests.

Results: Of the 298 patients, 59.4% were male, with a median age of 57 years. The cohort included PV (32.5%), ET (35.2%), PMF (8.7%), and MPN-u (23.5%). Hydroxyurea was used in 158 patients, while 126 patients were followed without cytoreductive therapy. Significant reductions in leukocyte and neutrophil counts were observed in the hydroxyurea group at months 0-3, 0-6, and 0-12 ($p<0.001$). NLR decreased significantly at months 0-3 and 0-6, while SII showed significant reductions at months 0-3, 0-6, and 0-12. CRP and LDH levels remained unchanged. No significant inflammatory changes were detected in patients not receiving hydroxyurea.

Conclusion: Hydroxyurea treatment was associated with early reductions in inflammatory indices in BCR-ABL-negative MPN patients, possibly reflecting either its myelosuppressive or its potential anti-inflammatory effects. Further prospective studies incorporating cytokine profiling are needed to clarify the mechanisms underlying hydroxyurea's impact on inflammation.

Keywords: Hydroxyurea, BCR-ABL-negative myeloproliferative neoplasms, systemic inflammation, neutrophil-to-lymphocyte ratio, systemic immune-inflammation index

Introduction

Myeloproliferative neoplasms (MPNs) comprise a heterogeneous group of clonal hematopoietic disorders characterized by dysregulated proliferation of myeloid lineage cells within the bone marrow (1). These disorders are traditionally categorized based on the predominant cell lineage involved and include polycythemia vera (PV), essential thrombocythemia (ET), and primary myelofibrosis (PMF). Following the identification of the Philadelphia chromosome and the Breakpoint Cluster Region- Abelson murine leukemia viral oncogene homolog 1 (BCR-ABL) fusion gene, MPNs lacking this molecular abnormality have been classified as BCR-ABL-negative entities (1).

Driver mutations involving Janus kinase 2 (JAK2), calreticulin (CALR), and the thrombopoietin receptor (MPL) play a central role in disease pathogenesis by promoting constitutive activation of intracellular signaling pathways (2). These molecular alterations not only drive clonal expansion but also contribute to a pro-inflammatory microenvironment.

Beyond uncontrolled myeloid proliferation, MPNs are associated with a spectrum of clinical complications, including extramedullary hematopoiesis, leukemic transformation, and progressive bone marrow fibrosis (3). Increasing evidence suggests that chronic inflammation is a fundamental component of MPN biology. Malignant and non-malignant cells within the tumor microenvironment interact to sustain the release



Address for Correspondence: Öğuz Altunok, MD, University of Health Sciences Türkiye, İstanbul Bakırköy Dr. Sadi

Konuk Training and Research Hospital, Clinic of Oncology, İstanbul, Türkiye

E-mail: altunok.06@gmail.com ORCID ID: orcid.org/0000-0002-7278-1307

Cite this article as: Altunok O, Serin İ, Yokuş O. Effects of hydroxyurea therapy on inflammatory markers and indices in patients with BCR-ABL negative myeloproliferative neoplasms. İstanbul Med J. 2026; 27(4): 320-324

Received: 24.02.2026

Accepted: 10.08.2026

Publication Date: 30.10.2026



©Copyright 2026 by the University of Health Sciences Türkiye, İstanbul Training and Research Hospital/İstanbul Medical Journal published by Galenos Publishing House.
Licensed under a Creative Commons Attribution-NonCommercial-NoDerivatives 4.0 (CC BY-NC-ND) International License

of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor- α (TNF- α), which in turn contribute to symptom burden and disease progression (4,5). This persistent inflammatory milieu has been linked to constitutional symptoms and fibrotic evolution.

Hydroxyurea remains one of the most frequently utilized cytoreductive agents in the management of MPNs. Its mechanism of action is primarily mediated through inhibition of ribonucleotide reductase, leading to depletion of deoxyribonucleotide pools and interruption of DNA synthesis during the S phase of the cell cycle (6). However, prolonged exposure or higher cumulative doses may result in increased oxidative stress and cytotoxic effects, ultimately causing bone marrow suppression and cytopenias (7).

Although hydroxyurea has long been established as a cornerstone in the treatment of MPNs, its influence on systemic inflammation remains incompletely understood. Evidence from studies in sickle cell disease suggests that hydroxyurea may modulate inflammatory pathways by reducing pro-inflammatory cytokines such as TNF- α while enhancing anti-inflammatory mediators such as IL-10 (8). Nevertheless, data specifically addressing this relationship in MPN patients are limited.

In the present study, we investigated the impact of hydroxyurea on systemic inflammatory status in patients with BCR-ABL-negative MPNs by evaluating commonly used inflammatory indices, including the neutrophil-to-lymphocyte ratio (NLR) and the systemic immune-inflammation index (SII). These indices, derived from routine hematologic parameters, have emerged as accessible and reproducible markers of systemic inflammation and have been increasingly utilized in both prognostic and predictive settings (9).

Methods

This retrospective study included patients admitted to the hematology outpatient clinic between January 1, 2010, and January 1, 2022. Patients were classified as PV, ET, PMF, or MPN-unclassifiable (MPN-u) according to the 2016 World Health Organization criteria. Baseline demographic and clinical data, including diagnosis, age at diagnosis, gender, underlying genetic mutations, and treatment preferences, were recorded. Laboratory parameters, such as neutrophil, lymphocyte, leukocyte and platelet counts, C-reactive protein (CRP), and lactate dehydrogenase (LDH), were evaluated at 0, 3, 6, and 12 months and compared across these time points. Changes in NLR and SII, derived from these values, were also monitored. Analysis of treatment preferences revealed that patients were either under active surveillance or were receiving cytoreductive therapy, including hydroxyurea, anagrelide, or ruxolitinib. The formula has been calculated as follows: NLR: neutrophil count/lymphocyte count (9) and SII: (neutrophil count x platelet count)/lymphocyte count (10).

Ethical Approval

Ethical approval was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Institutional Review Board (approval number: 328; date: 27 October 2022), and the study was performed in accordance with the Declaration of Helsinki. All participants provided written informed consent prior to participation.

Inclusion Criteria

- Patients aged ≥ 18 years were eligible for inclusion.
- Patients diagnosed with BCR-ABL negative MPN in our clinic
- Patients who had completed at least one year of follow-up and treatment in our clinic

Exclusion Criteria

- Patients younger than 18 years or with pregnancy
- Patients diagnosed with BCR-ABL positive MPN
- Patients with another disease or on medication affecting the systemic inflammatory response
- Patients without regular follow-up for at least one year

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 25.0 (IBM Corp., Armonk, NY, USA). The Shapiro-Wilk test was applied to assess the normality of patient data. For comparisons between two groups, the Mann-Whitney U test was used, while comparisons among three or more groups were performed using the Kruskal-Wallis test, followed by Dunn-Bonferroni post-hoc correction. For within-group comparisons of repeated measurements across the four time points (baseline, 3, 6, and 12 months), the Friedman test was used. When the Friedman test was significant, pairwise comparisons between time points were performed using the Wilcoxon signed-rank test, and p values were adjusted for multiple comparisons using the Bonferroni correction. Two-sided $p < 0.05$ was considered statistically significant.

Results

Of the 298 patients included in our study, 177 were male (59.4%) and 121 were female (40.6%). The median age at diagnosis was 57 years (range: 19.2-82.4). When divided into subgroups, the patients were classified as follows: 97 (32.5%) as PV, 105 (35.2%) as ET, 26 (8.7%) as PMF, and 70 (23.5%) as MPN-u. Analysis of treatment regimens showed that 126 patients were under active surveillance without cytoreductive therapy, whereas 158 patients were treated with hydroxyurea, 11 with anagrelide, and 3 with ruxolitinib (Table 1).

Genetic mutation results were obtained for 144 of the 298 BCR-ABL-negative MPN patients included in our study. Among them, 142 patients carried the JAK2 V617F mutation; 1 patient in the ET group had the MPL mutation, and 1 patient in the unclassified group had the CALR mutation.

When patients receiving cytoreductive therapy were stratified into those treated with hydroxyurea and those not, a statistically significant reduction in leukocyte and neutrophil counts was observed in the hydroxyurea group over months 0-3, 0-6, and 0-12 ($p < 0.001$). In contrast, no significant reductions were detected between 3 and 6, 3 and 12, and 6 and 12 months.

Upon evaluation of inflammatory indices, the NLR showed a statistically significant decrease from month 0 to month 3 and from month 0 to month 6 in patients receiving hydroxyurea ($p<0.001$ and $p=0.01$). Analysis of SIII showed a significant decrease in the hydroxyurea group at months 0-3, 0-6, and 0-12 ($p<0.001$, $p<0.05$, and $p<0.05$) (Graphics 1 and 2). However, no significant changes were found in CRP and LDH levels within the hydroxyurea-treated group ($p>0.05$).

No statistically significant decrease was found in leukocyte, neutrophil, CRP, LDH, NLR, and SIII values in patients who were under active follow-up or who received cytoreductive therapies other than hydroxyurea ($p>0.05$).

Discussion

In our study, which included 298 BCR-ABL–negative MPN patients, the cohort was classified into the following subgroups: PV (32.5%), ET

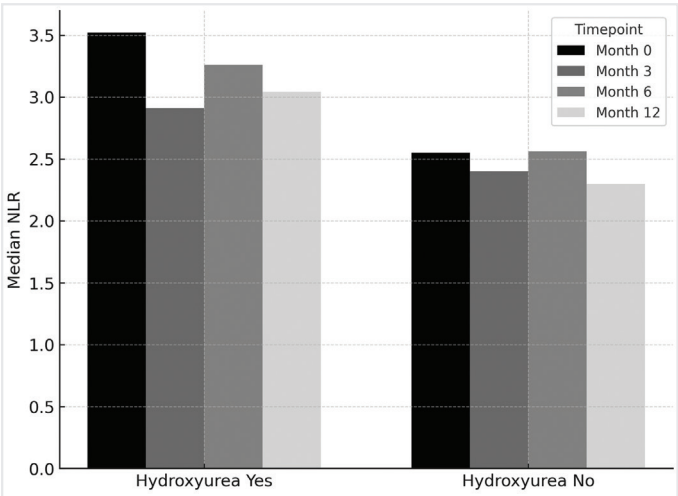
(35.2%), PMF (8.7%), and MPN-unclassified (23.5%). While 126 patients were followed without cytoreductive therapy, the remaining patients mostly received hydroxyurea, and a smaller number received anagrelide or ruxolitinib. Among 144 patients with available genetic data, the JAK2 V617F mutation was found in 142; only one MPL mutation and one CALR mutation were detected. Hydroxyurea treatment led to significant reductions in leukocyte and neutrophil counts at months 0-3, 0-6, and 0-12, and significant decreases in NLR and SIII during early follow-up, although CRP and LDH levels remained unchanged. This result suggests that the neutropenic effect caused by hydroxyurea is more prominent during the early stages of treatment. No significant changes were found in inflammatory indices in patients who were followed without treatment or who received treatments other than hydroxyurea.

It is known that chronic inflammation plays an important role in the pathophysiology of abnormal clonal proliferation, which forms the basis of MPNs (11). Somatic mutations underlying abnormal clonal proliferation such as JAK2 (V617F and exon12), MPL and CALR continuously activate signaling receptor pathways that trigger inflammatory responses (12). The continuous activation of these signaling receptor pathways plays a role in disease progression and development of constitutional symptoms through the release of inflammatory cytokines from both neoplastic cells and normal cells (13). In addition, inflammation is also involved in the development of premature atherosclerosis and thrombotic events in these patients (13). Therefore, controlling the inflammatory microenvironment is an important therapeutic goal in the MPNs (12,13).

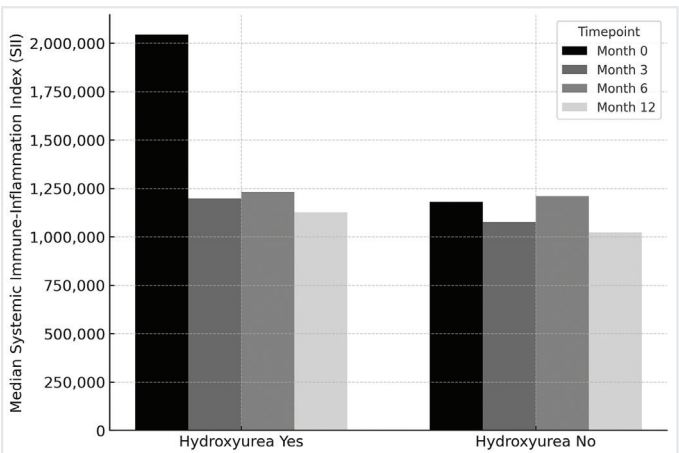
In our study, we investigated the effects of hydroxyurea in the MPN cohort, particularly its anti-inflammatory properties. A literature review indicates that similar investigations have been conducted in patients with sickle cell anemia. In the study conducted by Lanaro and colleagues, it was demonstrated that hydroxyurea treatment in the sickle cell anemia group resulted in a decrease in TNF-alpha levels, while leading to an increase in IL-10 levels, an anti-inflammatory cytokine (8). In an *in vitro* endothelial model carrying the JAK2 V617F mutation, it has been demonstrated that HU treatment prevents thrombosis development by

Table 1. Distribution of patients included in the study according to patient characteristics		
	n	%
Gender		
Male	177	59.4%
Female	121	40.6%
Diagnosis		
PV	97	32.5%
ET	105	35.2%
PMF	26	8.7%
MPN-u	70	23.5%
Treatment		
Surveillance	126	42.3%
Hydroxyurea	158	53%
Anagrelide	11	3.7%
Ruxolitinib	3	1%
Total	298	100%

PV: Polycythemia vera, ET: Essential thrombocythemia, PMF: Primary myelofibrosis, MPN-u: Myeloproliferative neoplasm-unclassifiable



Graphic 1. Median NLR at baseline and at months 3, 6, and 12 according to hydroxyurea treatment. In patients receiving hydroxyurea, NLR decreased significantly from baseline to month 3 ($p<0.001$) and from baseline to month 6 ($p=0.010$), whereas the baseline-to-month-12 difference was not statistically significant. No significant longitudinal changes were observed in patients not receiving hydroxyurea. NLR: Neutrophil-to-lymphocyte ratio



Graphic 2. Median SIII at baseline and at months 3, 6, and 12 according to hydroxyurea treatment. In patients receiving hydroxyurea, SIII decreased significantly from baseline to month 3 ($p<0.001$), to month 6 ($p<0.05$), and to month 12 ($p<0.05$). No significant longitudinal changes were observed in patients not receiving hydroxyurea

reducing P-selectin expression on the endothelium (14,15). In a study similar to ours that evaluated the NLR, the parameters of 35 children diagnosed with sickle cell anemia who were monitored while receiving hydroxyurea treatment for one year and those of 20 healthy controls were examined. It was observed that hydroxyurea treatment resulted in a significant decrease in NLR, accompanied by a concurrent reduction in inflammatory cytokine levels (15,16). In a different study, the effectiveness of hydroxyurea was evaluated in adult patients with sickle cell anemia by examining two distinct cohorts: those receiving hydroxyurea and those not receiving hydroxyurea. The hydroxyurea cohort was further divided into two subgroups based on dosage: individuals receiving a daily dose of 1 gram and those receiving a daily dose of 1.5–2 grams. Levels of inflammatory markers (myeloperoxidase, TNF- α , and IL-10) and oxidative markers (superoxide dismutase, glutathione peroxidase, and malondialdehyde) were significantly altered ($p < 0.05$) in these cells, demonstrating notable differences between the hydroxyurea subgroups and the non-hydroxyurea group. Treatment with HU restored the levels of all markers to concentrations similar to those observed in healthy individuals, indicating a positive dose-effect relationship (16). In a study of patients with sickle cell anemia, researchers analyzed the association between monocyte subsets and hydroxyurea treatment. Significant alterations in monocyte subsets were observed, with classical monocytes (CD14⁺⁺CD16⁻) being highly prevalent in individuals not receiving hydroxyurea, whereas those with a patrolling phenotype (CD14^{dim}CD16⁺) were more abundant in patients undergoing therapy. Furthermore, hydroxyurea was found to reduce the production of TNF- α , IL1- β , IL-6 and IL-8 (17).

A review of the literature shows that the number of studies investigating the relationship between hydroxyurea and inflammation, particularly in MPNs, is limited. In this research, MPN patients who were started on hydroxyurea treatment experienced an early decrease in neutrophil count, NLR, and SII. It is known that hydroxyurea causes myelosuppression through inhibition of DNA synthesis, which may lead to neutropenia, and that this side effect can resolve upon discontinuation of the drug (18,19). Thrombotic events are common complications in MPNs and arise through a complex interplay of blood cell activation, endothelial dysfunction, inflammation, and coagulation abnormalities. Leukocytes are key drivers of this thromboinflammatory process, releasing pro-inflammatory and pro-thrombotic mediators that amplify clot formation (19). Hydroxyurea has been shown to reduce thrombosis, particularly in high-risk ET and when combined with aspirin in MPNs (20,21). Therefore, its influence on inflammatory markers is clinically important. In this context, our study evaluates the effect of hydroxyurea on inflammatory parameters, changes in which may contribute to its protective role against thrombotic complications.

The observed reductions in NLR and SII may suggest attenuation of the circulating inflammatory milieu during hydroxyurea treatment (10). However, neutrophils constitute the numerator of both indices, while platelet counts are also incorporated into the calculation of SII. Therefore, the observed changes may largely represent a mathematical consequence of hydroxyurea-induced cytoreduction and myelosuppression rather than an independent anti-inflammatory effect (19). The absence of a significant change in CRP further limits

the interpretation of these findings as evidence of a systemic anti-inflammatory response. Although previous studies have reported that hydroxyurea may modulate inflammatory cytokines and immune-cell subsets (18), the present data cannot distinguish true immunomodulation from the numerical effects of reduced circulating blood cell counts. Moreover, thrombotic events, symptom burden, disease progression, and survival outcomes were not evaluated. Accordingly, these findings should be interpreted as changes in cell-count-derived inflammatory indices rather than definitive evidence of an independent anti-inflammatory effect or of clinical benefit.

We believe that, to more clearly demonstrate the impact of hydroxyurea on inflammation in patients with MPNs, future studies should evaluate inflammatory markers and cytokine profiles concurrently throughout the course of treatment in larger patient cohorts. Such comprehensive and longitudinal assessments will not only help clarify the mechanisms underlying hydroxyurea's anti-inflammatory effects, but also contribute valuable insights to future research and the development of more targeted therapeutic strategies.

Study Limitations

This study has several limitations that should be acknowledged. First, the retrospective study design inherently limits the ability to establish causal relationships between inflammatory indices and clinical outcomes. Second, as the analysis was conducted at a single institution, the findings may not be fully generalizable to broader, more diverse patient populations.

Although inflammatory parameters were assessed at predefined time points, potential confounding variables that could influence systemic inflammatory status may not have been fully controlled. The absence of detailed longitudinal cytokine profiling further restricts the ability to comprehensively interpret the underlying biological mechanisms.

Conclusion

Finally, molecular and genetic data were not uniformly available for all patients, which may have limited the ability to perform a more in-depth evaluation of disease heterogeneity and its potential impact on inflammatory markers.

Ethics

Ethics Committee Approval: Ethical approval was obtained from the University of Health Sciences Türkiye, İstanbul Training and Research Hospital Institutional Review Board (approval number: 328; date: 27 October 2022), and the study was performed in accordance with the Declaration of Helsinki.

Informed Consent: All participants provided written informed consent prior to participation.

Footnotes

Authorship Contributions: Surgical and Medical Practices - O.A., I.S., O.Y.; Concept - O.A., I.S.; Design - O.A., O.Y.; Data Collection or Processing - O.A., I.S., O.Y.; Analysis or Interpretation - O.A., I.S., O.Y.; Literature Search - O.A., Writing - O.A.

Conflict of Interest: No conflict of interest was declared by the authors.

Financial Disclosure: The authors declared that this study received no financial support.

References

- Spivak JL. Myeloproliferative neoplasms. *N Engl J Med*. 2017; 376: 2168-81
- Barbui T, Thiele J, Gisslinger H, Kvasnicka HM, Vannucchi AM, Guglielmelli P, et al. The 2016 WHO classification and diagnostic criteria for myeloproliferative neoplasms: document summary and in-depth discussion. *Blood Cancer J*. 2018; 8: 15.
- Genthon A, Killian M, Mertz P, Cathebras P, Gimenez De Mestral S, Guyotat D, et al. Les myéofibroses [Myelofibrosis: A review]. *Rev Med Interne*. 2021; 42: 101-9. French.
- Lussana F, Rambaldi A. Inflammation and myeloproliferative neoplasms. *J Autoimmun*. 2017; 85: 58-63.
- Mendez Luque LF, Blackmon AL, Ramanathan G, Fleischman AG. Key role of inflammation in myeloproliferative neoplasms: instigator of disease initiation, progression. and symptoms. *Curr Hematol Malig Rep*. 2019; 14: 145-53.
- Musiak MW, Rybaczek D. Hydroxyurea-the good, the bad and the ugly. *Genes (Basel)*. 2021; 12: 1096.
- Huang ME, Facca C, Fatmi Z, Baille D, Bénakli S, Vernis L. DNA replication inhibitor hydroxyurea alters Fe-S centers by producing reactive oxygen species in vivo. *Sci Rep*. 2016; 6: 29361.
- Lanaro C, Franco-Penteado CF, Albuquerque DM, Saad STO, Conran N, Costa FF. Altered levels of cytokines and inflammatory mediators in plasma and leukocytes of sickle cell anemia patients and effects of hydroxyurea therapy. *J Leukoc Biol*. 2009; 85: 235-42.
- Zahorec R. Neutrophil-to-lymphocyte ratio, past, present and future perspectives. *Bratisl Lek Listy*. 2021; 122: 474-88.
- Wu Y, Huang Y, Wu Y, Sun J, Xie Q, Yin G. Systemic immune-inflammation index as a versatile biomarker in autoimmune disorders: insights from rheumatoid arthritis, lupus, and spondyloarthritis. *Front Immunol*. 2025; 16: 1621209.
- Hasselbalch HC. Perspectives on chronic inflammation in essential thrombocythemia, polycythemia vera, and myelofibrosis: is chronic inflammation a trigger and driver of clonal evolution and development of accelerated atherosclerosis and second cancer? *Blood*. 2012; 119: 3219-25.
- Hermouet S, Bigot-Corbel E, Gardie B. Pathogenesis of myeloproliferative neoplasms: role and mechanisms of chronic inflammation. *Mediators Inflamm*. 2015; 2015: 145293.
- Klampfl T, Gisslinger H, Harutyunyan AS, Nivarthi H, Rumi E, Milosevic JD, et al. Somatic mutations of calreticulin in myeloproliferative neoplasms. *N Engl J Med*. 2013; 369: 2379-90.
- Fleischman AG. Inflammation as a driver of clonal evolution in myeloproliferative neoplasm. *Mediators Inflamm*. 2015; 2015: 606819.
- Guy A, Gourdou-Latyszenok V, Le Lay N, Peghaire C, Kilani B, Dias JV, et al. Vascular endothelial cell expression of JAK2^{V617F} is sufficient to promote a pro-thrombotic state due to increased P-selectin expression. *Haematologica*. 2019; 104: 70-81.
- Zahran AM, Nafady A, Saad K, Hetta HF, Abdallah AM, Abdel-Aziz SM, et al. Effect of hydroxyurea treatment on the inflammatory markers among children with sickle cell disease. *Clin Appl Thromb Hemost*. 2020; 26: 1076029619895111.
- Pedrosa AM, Leal LKAM, Lemes RPG. Effects of hydroxyurea on cytotoxicity, inflammation and oxidative stress markers in neutrophils of patients with sickle cell anemia: dose-effect relationship. *Hematol Transfus Cell Ther*. 2021; 43: 468-75.
- Guarda CC, Silveira-Mattos PSM, Yahouédéhou SCMA, Santiago RP, Aleluia MM, Figueiredo CVB, et al. Hydroxyurea alters circulating monocyte subsets and dampens its inflammatory potential in sickle cell anemia patients. *Sci Rep*. 2019; 9: 14829.
- Yarbro JW. Mechanism of action of hydroxyurea. *Semin Oncol*. 1992; 19: 1-10.
- Liu Y, Wang Y, Huang G, Wu S, Liu X, Chen S, et al. The role of leukocytes in myeloproliferative neoplasm thromboinflammation. *J Leukoc Biol*. 2024; 115: 1020-8.
- Cortelazzo S, Finazzi G, Ruggeri M, Vestri O, Galli M, Rodeghiero F, et al. Hydroxyurea for patients with essential thrombocythemia and a high risk of thrombosis. *N Engl J Med*. 1995; 332: 1132-6.