Incidental changes in hemoglobin levels in patients with myelofibrosis receiving treatment with sodium-glucose co-transporter-2 inhibitors

Sodium-glucose co-transporter-2 inhibitors (SGLT-2I) (also known as gliflozins or flozins) are increasingly prescribed for diabetes mellitus, heart failure and chronic kidney disease.[1] Food and Drug Administration (FDA)-approved drugs within the SGLT-2I class, bexagliflozin, canagliflozin, dapagliflozin, empagliflozin, ertugloflozin, and sotagliflozin offer cardio-protection and enhance erythropoiesis through inter-related mechanisms.[2] The physiology of SGLT2-I-induced erythro-cytosis is multifactorial; potential mechanisms include: i) increased erythropoietin (Epo) production; ii) suppression of hepcidin and modulation of iron metabolism; and iii) hemo-concentration.[3] In placebo-controlled studies, empagliflozin demonstrated a dose-dependent increase in hemoglobin (Hb) and hematocrit (Hct) levels, with a median increase in Hct of 4.8±5.5% and 5.0±5.3% with empagliflozin 10 mg and 25 mg, respectively, *versus* 0.9±4.7% with placebo.[4] SGLT-2I have also been shown to ameliorate anemia in patients with chronic kidney disease; in a post-hoc analysis of the Cana-gliflozin and Renal Events in Diabetes with Established Ne-phropathy Clinical Evaluation (CREDENCE)[5] and Dapagliflozin in Patients with Chronic Kidney Disease (DAPA-CKD) trials,[6] increase in Hct was 2.4% and 2.3% higher in the canagliflozin and dapagliflozin arms, respectively, compared to placebo. Moreover, resolution of anemia was noted in a higher pro-portion of patients on dapagliflozin than placebo (53.3% *vs*. 29.4%). In the light of these observations, we postulate that SGLT-2I might stimulate erythropoiesis and improve anemia in chronic myeloid malignancies such as myelofibrosis (MF).[7-9] Accordingly, in the current study, our primary objective was to evaluate the impact of SGLT-2I therapy on Hb levels and anemia-related outcomes in patients with MF.

After approval by the Institutional Review Board for minimal risk research protocol, the Mayo Clinic myeloproliferative neoplasm (MPN) clinical database was queried to identify patients with primary or secondary MF, prescribed SGLT2-I for diabetes mellitus, heart failure or chronic kidney disease, following established diagnosis of MF.[10] The time of SGLT-2I initiation was considered as baseline and for each patient, baseline Hb, changes in Hb, and thrombotic events during SGLT-2I treatment were recorded. Therapeutic interventions for MF including timing of initiation and discontinuation of cytoreductive agents were carefully documented.

A total of 16 patients with MF (primary MF [PMF], N=12; post-es-sential thrombocythemia MF [post-ET MF], N=4) received treatment with empagliflozin (N=10), dapagliflozin (N=4), or canagliflozin (N=2) between July 2019 and March 2024. Median age was 74 years; 56% were males. *JAK2*V617F mutation was detected in 8 (50%) cases: *CALR* mutation in 5 (31%), *MPL* in 2 (13%) cases, while one (6%) case was triple-negative. A history of thrombosis before SGLT-2I use was documented in 8 (50%) patients which included 4 arterial (25%) and 4 venous (25%) events. Seven (44%) patients received cytoreductive therapy, including hydroxyurea (N=2), ruxolitinib (N=4), and momelotinib (N=1); 11 (69%) and 6 (38%) patients were also on antiplatelet therapy and systemic anticoagulation, respectively. Table 1 provides detailed clinical and laboratory characteris-tics of 16 patients with MF started on SGLT-2I at a median of 12 months (range: 2-73 months) after MF diagnosis. Baseline median Hb value at the time of initiation of SGLT-2I was 11 g/dL (range: 8-15); 6 (38%) patients had Hb <10 g/dL includ-ing one case (6%) with transfusion-dependent anemia. At a median treatment duration of 11.5 months (range: 2-73), 2 (13%) patients experienced venous thrombosis while receiv-ing SGLT-2I therapy; both events were chronic pulmonary thromboembolism secondary to pulmonary hypertension. Median follow-up from MF diagnosis and SGLT-2I initiation was four years (range: 1-18 years) and 1.2 years (range: 0.3-6.1 years), respectively, during which 4 deaths and no leukemic transformations were recorded.

Table 2 and Figure 1 highlight Hb changes from baseline to post-treatment Hb levels in all 16 patients with MF receiving SGLT-2I. Fourteen (88%) patients experienced an increase in Hb levels after initiation of SGLT-2I, with an improvement in Hb of ≥1 g/dL in 9 (54%) patients. An increase in Hb of 1.5 g/dL or greater was documented in 6 (38%) cases (Patients 2, 5, 8, 9, 11, and 15), and 3 (19%) patients displayed an increase in Hb of between 1 and 1.4 g/dL (Patients 4, 7, and 13). Among 6 anemic patients with baseline Hb <10 g/dL (Patients 2, 4, 9, 11, 13, and 14), 3 (50%) showed an improvement in Hb of ≥1.5 g/dL, and 2 (33%) displayed an increase in Hb of 1 g/dL. On the other hand, 2 (12%) patients did not experience any improvements in Hb; Patient 3 had a decrease in Hb and Patient 14 remained transfusion-dependent during SGLT-2I therapy. Details on hematologic parameters and the clinical course of patients with an improvement in Hb of ≥1 g/dL are provided below.

Patient 2, a 77-year-old female with *JAK2*V167F-mutated post-ET MF with no history of thrombosis and not on cy-toreductive therapy, received canagliflozin 100 mg daily for diabetes mellitus and chronic kidney disease. Baseline Hb and Hct were 8.2 g/dL and 27.5%, respectively; one month after initiation of SGLT-2I, Hb and Hct levels peaked at 10.2 g/dL and 33.5%, respectively. Shortly thereafter, two weeks after achieving peak Hb and Hct levels, canagliflozin was

discontinued due to pancreatic cysts, and Hb after stopping SGLT-2I was 9.3 g/dL.

Patient 4, a 79-year-old male with *JAK2*V167F-mutated PMF and a history of venous thrombosis, received empagliflozin 10 mg daily for heart failure with reduced ejection fraction (HFrEF) and diabetes mellitus. Baseline Hb and Hct were 9.4 g/dL and 28%, respectively; four months after initiation of SGLT-2I, Hb and Hct levels peaked at 10.4 g/dL and 31.8%, respectively, and these levels were sustained for 25 months.

Patient 5, a 72-year-old male with *JAK2*V167F-mutated PMF, received dapagliflozin 5 mg daily for diabetes mellitus and chronic kidney disease. Baseline Hb and Hct were 10.9 g/dL and 34.7%, respectively; 15 months after initiation of SGLT-2I, Hb and Hct levels peaked at 13.1 g/dL and 42.2%, respectively, and these levels were sustained for nine months. Dapagliflozin was discontinued due to acute kidney injury, and Hb within one month of stopping the drug was 9.5 g/dL. It is to be noted that he had received intravenous iron two weeks prior to achieving peak Hb and Hct levels. Also, he had been started on ruxolitinib 5 mg twice daily three days prior to peak Hb.

Patient 7, a 60-year-old female with *JAK2*V167F-mutated PMF, on hydroxyurea 1,000 mg daily, received dapagliflozin 10 mg daily for HFrEF. Baseline Hb and Hct were 14.7 g/dL and 45.9%, respectively; one month after initiation of SGLT-2I, Hb and Hct levels peaked at 16.1 g/dL and 49.4%, respectively. Thereafter, eight weeks after achieving peak Hb and Hct levels, dapagliflozin was discontinued, although the reasons for this remain unclear.

Patient 8, a 65-year-old male with *MPL*-mutated PMF received empagliflozin 25 mg daily for diabetes mellitus. Baseline Hb

Table 1. Clinical and laboratory characteristics of 16 patients with myelofibrosis at initiation of sodium glucose co-transporter-2 inhibitors.

Variables at time of SGLT-2I	N=16
Age in years, median (range)	74 (56-88)
Male gender, N (%)	9 (56)
Driver mutation, N (%)	
JAK2	8 (50)
CALR	5 (31)
MPL	2 (13)
MPN type, N (%)	
MF	12 (75)
Post-ET MF	4 (25)
Time from MF diagnosis to SGLT-2I in months, median (range)	5 (0-206)
SGLT-2I and dose, N (%)	
Canagliflozin 100 mg	1 (6)
Canagliflozin 150 mg	1 (6)
Dapagliflozin 5 mg	2 (13)
Dapagliflozin 10 mg	2 (13)
Empagliflozin 10 mg	5 (31)
Empagliflozin 12.5 mg	1 (6)
Empagliflozin 25 mg	4 (25)
Additional cause for erythrocytosis, N (%)	
Obstructive sleep apnea	6 (38)
Thrombosis history,[a] N (%)	
Major arterial thrombosis before SGLT- 2I	4 (25)
Major venous thrombosis before SGLT-2I	4 (25)
Splenomegaly, N (%)	10 (63)
Baseline Hb, g/dL, median (range)	11 (8-15)
<10 g/dL, N (%)	6 (38)
Below reference range,[b] N (%)	16 (100)
Baseline Hct, %, median (range)	33 (24-46)
<30%, N (%)	4 (25)
Below reference range,[c] N (%)	16 (100)

[a]Cerebrovascular accident, myocardial infarction, deep venous thrombosis, pulmonary embolism. [b]Hemoglobin (Hb) reference range: females 11.6-15 g/dL, males 13.2-16.6 g/dL. [c]Baseline hematocrit (Hct) reference range: females 35.5-44.9%, males 38.3-48.6%. ET: essential thrombocythemia; MF: myelofibrosis; MPN: myeloproliferative neoplasms; N: number; SGLT-2I: sodium glucose co-transporter-2 inhibitors.

Table 2. Clinical outcomes of 16 patients with myelofibrosis after initiation of sodium glucose co-transporter-2 inhibitors.

Outcomes after SGLT-2I therapy	
Increase in Hb/Hct, N (%)	14 (88)
Peak Hb, g/dL, median (range)	12 (8-16)
Male	12 (10-16)
Female	11 (8-16)
Peak Hct, %, median (range)	36 (24-50)
Male	38 (32-48)
Female	34 (24-50)
Change in Hb/Hct	
Change in Hb, g/dL, median (range)	1 (0-3)
Change in Hct, %, median (range)	4 (0-11)
Time to peak Hb/Hct in months, median (range)	6 (1-33)
Baseline leukocyte count, x10^9/L, median (range)	8 (5-22)
Leukocyte count at time of peak Hb, x10^9/L, median (range)	9 (8-24)
Baseline Plt count, x10^9/L, median (range)	361 (12-715)
Plt count at time of peak Hb, x10^9/L, median (range)	386 (15-666)
Serum erythropoietin, mIU/mL,[a] 7 patients evaluated, median (range)	52 (7-2,448)
Pretreatment serum erythropoietin, mIU/mL,[a] 3 patients evaluated, median (range)	52 (26-55)
Serum ferritin, mcg/L,[b] 16 patients evaluated, median (range)	111 (20-3,266)
Treatment for MF, N (%)	
Antiplatelet therapy	11 (69)
Systemic anticoagulation	7 (44)
Cytoreductive therapy[Ω]	7 (44)
Darbepoetin alfa	2 (13)
SGLT-2I treatment duration in months, median (range)	12 (2-73)
Thrombosis during SGLT-2I therapy, N (%)	
Major arterial thrombosis	0
Major venous thrombosis	2 (13)

Hb: hemoglobin; Hct: hematocrit; MF: myelofibrosis; N: number; Plt: platelets; SGLT-2I: sodium glucose co-transporter-2 inhibitors. [Ω]Cytoreductive therapy: hydroxyurea (N=2), ruxolitinib (N=4), momelotinib (N=1). [a]Serum erythropoietin reference range: 2.6-18.5 mIU/mL. [b]Serum ferritin reference range: 24-336 mcg/L.

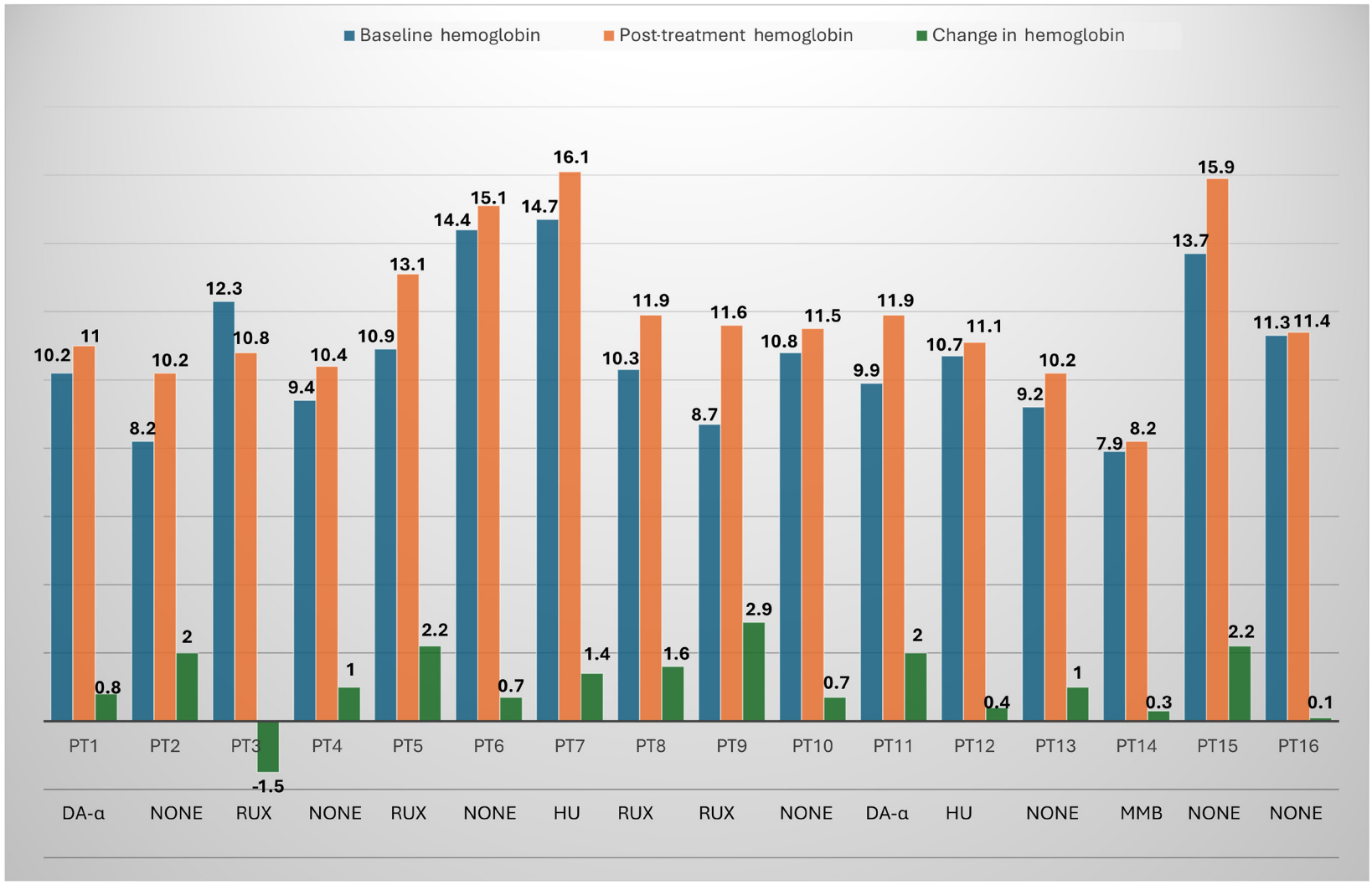


Figure 1. Baseline, hemoglobin (g/dL), post-treatment hemoglobin (%) and change in hemoglobin in 16 patients with myelofibrosis (MF) receiving sodium glucose co-transporter-2 inhibitors (SGLT-2I). DA-α; darbepoetin alfa; HU: hydroxyurea; PT: Patient; MMB: momelotinib; RUX: ruxolitinib.

and Hct were 10.3 g/dL and 30.9%, respectively; six months after initiation of SGLT-2I, Hgb and Hct levels peaked at 11.9 g/dL and 35.2%, respectively, and these levels were sustained for six months. He was started on ruxolitinib 5 mg twice daily ten days prior to peak Hb.

Patient 9, a 75-year-old male with *JAK2*V167F-mutated PMF and a history of venous thrombosis before and during SGLT-2I, received empagliflozin 10 mg daily for HFrEF. Baseline Hb and Hct were 8.7 g/dL and 27.7%, respectively; eight months after initiation of SGLT-2I Hb and Hct levels peaked at 11.6 g/dL and 38.4%, respectively. Notably, ruxolitinib 20 mg twice daily had been discontinued and he had been started on momelotinib 200 mg daily three months prior to peak Hb.

Patient 11, a 78-year-old male with *JAK2*V167F-mutated PMF and a history of arterial thrombosis was started on empagliflozin 10 mg daily for HFrEF. He was also receiving darbepoetin alfa 200 mcg every two weeks. Baseline Hb and Hct were 9.9 g/dL and 33.6%, respectively; six months after initiation of SGLT-2I, Hgb and Hct levels peaked at 11.9 g/dL and 37%, respectively, and these levels were maintained for five months. At that time, empagliflozin was discontinued due to gastrointestinal intolerance, and Hb one month after stopping the drug was 9.9 g/dL.

Patient 13, an 82-year-old female with *MPL*-mutated post-ET MF received dapagliflozin 5 mg daily for diabetes mellitus. Baseline Hb and Hct were 9.2 g/dL and 30.6%, respectively; 14 months after initiation of SGLT-2I, Hb and Hct levels peaked at 10.2 g/dL and 31.3%, respectively.

Patient 15, a 75-year-old male with *JAK2*V167F-mutated PMF and a history of arterial thrombosis, received empagliflozin 12.5 mg daily for diabetes mellitus. Baseline Hb and Hct were 13.7 g/dL and 43.4%, respectively; 28 months after initiation of SGLT-2I Hb and Hct levels peaked at 15.9 g/dL and 48.4%, respectively, and these levels were sustained for 30 months. Thereafter, empagliflozin was discontinued due to gastrointestinal intolerance, and Hb after stopping the drug was 13.5 g/dL.

SGLT-2I use in patients with MPN is understudied; a recent report on 11 patients with ET receiving SGLT-2I therapy showed consistent increments in Hb and Hct levels with a baseline median increase in Hb and Hct of 1.5 g/dL (range: 1-4) and 5.1% (range: 2.6-13.8), respectively.[11] A separate study described underlying *JAK2*-mutated MPN in 9 patients on SGLT-2I and highlighted 4 incidents of thrombotic complications.[12] The current series is the first to underline the erythropoietic activity of SGLT-2I in MF patients and suggests the therapeutic value of SGLT-2I for management of MF-related anemia. Hepcidin is up-regulated in MF, and SGLT-2I-induced suppression of hepcidin and modulation of iron metabolism likely contributes to the observed increase in Hb levels.[13] The majority of

patients experienced an increase in Hb levels after initiation of SGLT-2I with 5 patients reporting sustained Hb improvement of ≥1.5 g/dL for at least 12 weeks, including 2 patients not receiving concurrent therapy; most (80%) of these patients were male and all were *JAK2*-mutated. Moreover, among 6 patients with baseline anemia (Hb <10 g/dL), 5 (83%) showed improvement in Hb of at least 1 g/dL. With regard to drug safety, 2 venous thrombotic events occurred during SGLT2-1 use; both were unrelated to therapy and none of the patients experienced leukemic transformation. Incidentally, SGLT-2I use was associated with a lower incidence of acute myeloid leukemia in a population-based analysis of patients with diabetes mellitus receiving SGLT-2I (N=718,276) compared to dipeptidyl peptidase 4 inhibitors (N=1,159,112) (Hazard Ratio: 0.67; *P*<0.01).[14] Furthermore, several preclinical studies have provided evidence for potential anticancer effects of SGLT-2I.[15] Taken together, the current study suggests salutary effects of SGLT-2I on Hb levels in patients with MF; however, additional studies are required to better characterize the improvements in Hb level in the context of JAK inhibitors and other cytoreductive therapies.

Authors

Fnu Aperna, Ali K. Alsugair, Saubia Fathima, Ayalew Tefferi and Naseema Gangat

Division of Hematology, Mayo Clinic, Rochester, MN, USA

Correspondence:
N. GANGAT - gangat.naseema@mayo.edu

https://doi.org/10.3324/haematol.2024.286867

Received: October 28, 2024.
Accepted: November 21, 2024.
Early view: November 28, 2024.

©2025 Ferrata Storti Foundation
Published under a CC BY-NC license

Disclosures

NG has served on the Advisory Board for DISC Medicine and Agios. All of the other authors have no conflicts of interest to disclose.

Contributions

All authors designed the study, collected data, performed the analyses, wrote the paper, and reviewed the final draft for publication.

Data-sharing statement

All requests for data should be emailed to the corresponding author.

References

1. Braunwald E. Gliflozins in the management of cardiovascular disease. N Engl J Med. 2022;386(21):2024-2034.
2. Packer M. Mechanisms of enhanced renal and hepatic erythropoietin synthesis by sodium-glucose cotransporter 2 inhibitors. Eur Heart J. 2023;44(48):5027-5035.
3. Mazer CD, Hare GMT, Connelly PW, et al. Effect of empagliflozin on erythropoietin levels, iron stores, and red blood cell morphology in patients with type 2 diabetes mellitus and coronary artery disease. Circulation. 2020;141(8):704-707.
4. Zinman B, Wanner C, Lachin JM, et al. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373(22):2117-2128.
5. Oshima M, Neuen BL, Jardine MJ, et al. Effects of canagliflozin on anaemia in patients with type 2 diabetes and chronic kidney disease: a post-hoc analysis from the CREDENCE trial. Lancet Diabetes Endocrinol. 2020;8(11):903-914.
6. Koshino A, Schechter M, Chertow GM, et al. Dapagliflozin and anemia in patients with chronic kidney disease. NEJM Evid. 2023;2(6):EVIDoa2300049.
7. Gangat N, Abdallah M, Szuber N, et al. Sodium-glucose co-transporter-2 inhibitor use and JAK2 unmutated erythrocytosis in 100 consecutive cases. Am J Hematol. 2023;98(7):E165-E167.
8. Gangat N, Tefferi A. Sodium-glucose co-transporter-2 inhibitor use and erythrocytosis: assessment of risk and need for referral to haematology. Nephrol Dial Transplant. 2023;38(12):2670-2672.
9. Tefferi A. Primary myelofibrosis: 2023 update on diagnosis, risk-stratification, and management. Am J Hematol. 2023;98(5):801-821.
10. Arber DA, Orazi A, Hasserjian RP, et al. International Consensus Classification of Myeloid Neoplasms and Acute Leukemias: integrating morphologic, clinical, and genomic data. Blood. 2022;140(11):1200-1228.
11. Gangat N, Reichard K, Tefferi A. Sodium-glucose co-transporter-2 inhibitor treatment in essential thrombocythemia: impact on hemoglobin/hematocrit levels and outcomes among 11 consecutive patients. Am J Hematol. 2023;98(11):E298-E300.
12. Gangat N, Alkhateeb H, Reichard K, Tefferi A. Sodium-glucose co-transporter-2 inhibitor therapy and unmasking of JAK2-mutated myeloproliferative neoplasm: a Mayo Clinic series of nine consecutive cases. Am J Hematol. 2023;98(10):E276-E280.
13. Pardanani A, Finke C, Abdelrahman RA, Lasho TL, Tefferi A. Associations and prognostic interactions between circulating levels of hepcidin, ferritin and inflammatory cytokines in primary myelofibrosis. Am J Hematol. 2013;88(4):312-316.
14. Lee GY, Huang C, Ma KS-K. Lower incidence of leukemia in sodium glucose cotransporter-2 inhibitor-treated patients with type 2 diabetes mellitus: result from large real-world cohorts. Blood. 2023;142(Suppl 1):5172.
15. Dabour MS, George MY, Daniel MR, Blaes AH, Zordoky BN. The cardioprotective and anticancer effects of SGLT2 inhibitors. JACC CardioOncol. 2024;6(2):159-182.