Sodium-glucose co-transporter-2 inhibitor treatment-associated changes in hemoglobin level in anemic patients with myelodysplastic syndromes or myelodysplastic/myeloproliferative neoplasms

Sodium-glucose co-transporter-2 inhibitors (SGLT2i; canagliflozin, empagliflozin, dapagliflozin, ertugliflozin and sotagliflozin) are widely used for their beneficial effects on diabetes, heart failure, and chronic kidney disease. Multiple studies have reported SGLT2i treatment-emergent secondary erythrocytosis. In the EMPA-REG OUTCOME trial, median hematocrit (Hct) changes were 4.8±5.5% and 5.0±5.3% in the groups receiving empagliflozin 10 mg and 25 mg, respectively, compared to 0.9±4.7% in the placebo group.[1] A meta-analysis of 40 randomized clinical trials, involving 21,050 patients receiving SGLT2i treatment confirmed their dose-dependent erythropoietic effect, with a total weighted mean difference in Hct of 2.67% (95% confidence interval [CI]: 2.53-2.82).[2] We have previously shown that SGLT2i treatment-emergent erythrocytosis in patients without underlying myeloproliferative neoplasms (MPN) was not associated with a *JAK2* mutation and was not associated with increased risk of thrombosis.[3,4] On the other hand, such therapy, in the setting of an underlying occult[5] or overt[6] MPN might facilitate clonal erythrocytosis, sometimes associated with thrombotic complications. Conversely, anemic patients with myeloid neoplasms might benefit from the drug's erythropoietic effect. In the current retrospective study, we explored the latter possibility in anemic patients with myelodysplastic syndromes (MDS) or MDS/MPN.

After obtaining institutional review board approval, we conducted a retrospective Mayo Clinic database search for patients with diagnoses of MDS or MDS/MPN and concurrent use of any SGLT2i. The initial search produced 63 patients, of whom 23 were evaluable in terms of accurate time points of treatment with SGLT2i. In order to further minimize the impact of other confounding factors for adjudicating anemia response, an additional 12 patients were excluded because of either commencement of MDS- or MDS/MPN-directed therapy within the 3 months before or after starting treatment with SGLT2i or where treatment with SGLT2i predated the diagnosis of MDS or MDS/MPN. The final tally of evaluable cases was 11, of whom four were receiving stable doses of anemia-directed therapy (darbepoetin N=2, luspatercept N=1, azacitidine N=1) for >3 months prior to initiating SGLT2i and two were transfusion-dependent prior to starting treatment with SGLT2i. Hemoglobin (Hgb) and Hct levels were recorded at three time points: i) at baseline which is the time of SGLT2i treatment initiation, ii) at highest level achieved during SGLT2i treatment, and iii) at last follow up.

Among the 11 study patients (median age 77 years; range, 63-85; 72% males; Table 1), specific diagnosis was MDS-*SF3B1* in five patients, MDS with multilineage dysplasia in two, MDS/MPN-*SF3B1* and thrombocytosis in two, chronic myelomonocytic leukemia (CMML) in one, and MDS-del(5q) in one. Six (54%) patients were treatment-naive prior to SGLT2i initiation, four were on active chronic MDS-directed therapy, and one had a history of treatment with luspatercept and lenalidomide which were stopped prior to initiation of SGLT2i therapy. The four patients on active therapy were receiving stable doses of darbepoetin (N=2), luspatercept (N=1) or azacitidine (N=1). Molecular International Prognostic Scoring System for Myelodysplastic Syndromes (M-IPSS) scoring in these 11 patients included five with very low-risk disease, five low-risk and one moderate low-risk; three patients had therapy-related disease. The median values, at the time of SGLT2i treatment start, for leukocyte and platelet counts were $6.8x10^9$/L (range, 2.9-10) and $233x10^9$/L (range, 109-668), respectively; karyotype was normal in eight (72%) patients while next-generation sequencing revealed *SF3B1* mutation in seven (63%), *U2AF1* in two (18%), and *ASXL1* in another two (18%). Treatment with SGLT2i included empagliflozin 10 mg (N=9) and dapagliflozin 10 mg (N=2). Indications for treatment with SGLT2i included heart failure (N=8), diabetes (N=2), and chronic kidney disease (N=1). Table 1 summarizes patients and disease characteristics at the time of treatment start with SGLT2i.

At a median 10 months (range, 3-23) from the start of therapy with SGLT2i, none of the two patients who were transfusion-dependent responded. Among the remaining nine patients who were non-transfusion dependent, median Hgb/Hct levels at baseline (start of SGLT2i therapy), peak (highest level during SGLT2i therapy), and last follow-up were 9.6 g/dL/29.9% (range, 8.5-11.2/25.3-35.3), 10.8 g/dL/32.7 % (range, 10.4-12.4/31.3-38.5) and 10.4 g/dL/32.05% (range, 7.6-12.4/24.8-37.8), respectively (Table 1). Among the nine non-transfusion dependent patients, six (67%) had an increase in Hgb level of ≥1 g/dL, including three (33%) with an increase of ≥1.5 g/dL and two (22%) ≥2 g/dL (Figure 1). Among the six responders, four (67%) were treatment-naïve at the time of SGLT2i therapy initiation. Four (67%) of the

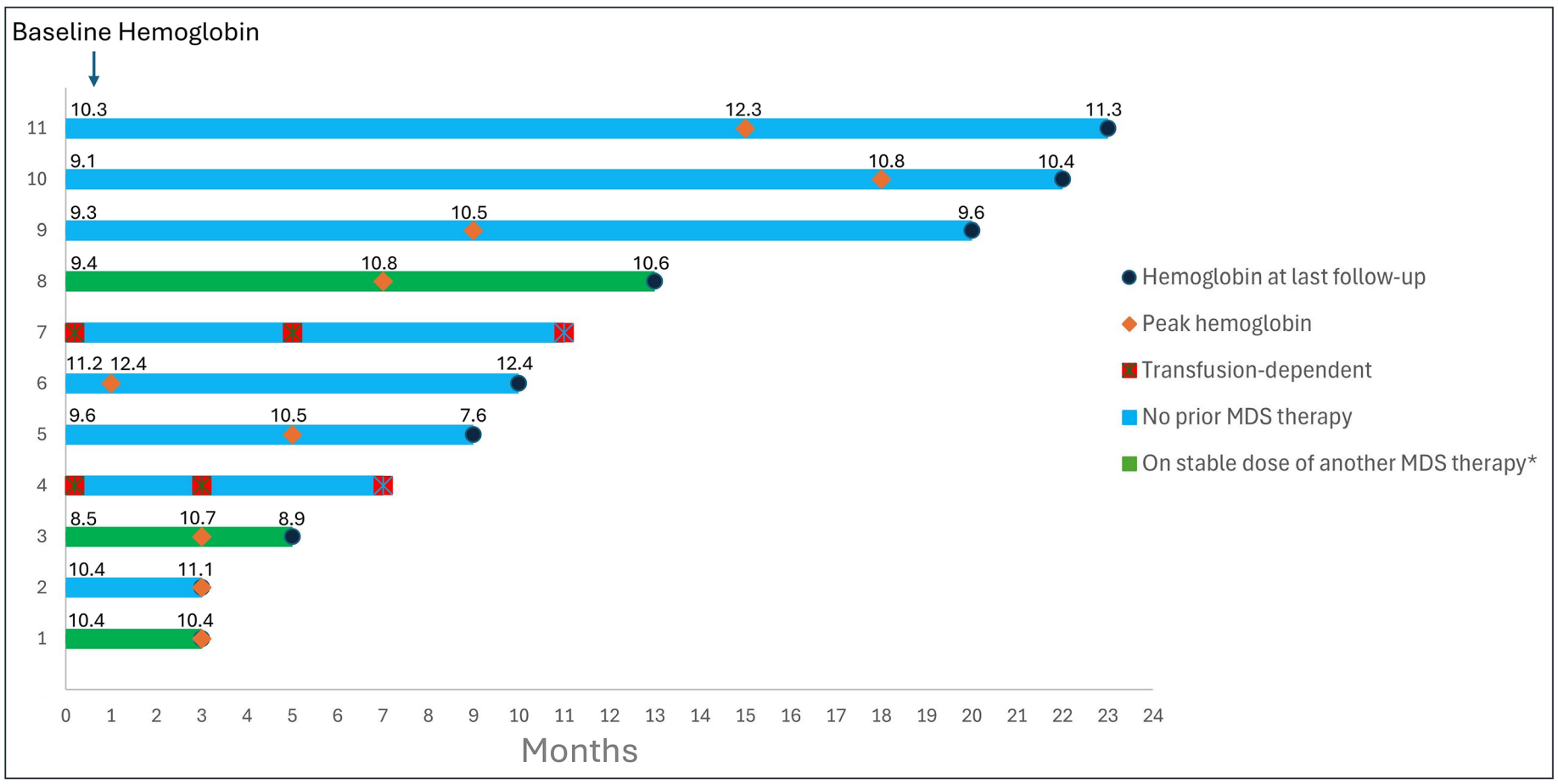
six treatment responders sustained their response at time of last follow-up with median duration of response at 17.5 months (range, 10-23). Median time to peak Hgb, among all nine non-transfusion-dependent patients, was 5 months (range, 1-18); median change in Hgb/Hct levels from baseline to peak was 1.2 g/dL/3.7% (range, 0-2.2/0.7-7.4) and from baseline to last follow-up was 0.7g/dL/2.1% (range, -2 to 1.3/-4.6 to 5.1). SGLT2i was discontinued in one patient (patient #10; Figure 1) due to diabetic ketoacidosis. At last follow-up, Hgb had decreased from 10.4 to 8.4 g/dL in 3 weeks after SGLT2i discontinuation. One patient had an increase in platelet count from 474 to 773x10^9/L during SGLT2i therapy. There were no accompanying changes in leukocyte counts. Anemia response did not correlate with either karyotype or mutations. Serum erythropoietin (Epo) levels were not systematically done but were available in five of the eleven study patients, all of whom were transfusion-independent; timing of testing was 4 months prior to SGLTi treatment initiation in two patients (patients 9 and 10 in Figure 1), 3 months before (patient 6), 2 months before (1 patient), and 1 week before (1 patient); median erythropoietin (EPO) level was 22.3 mIU/mL (range, 14.6-62.2); of these five informative cases, three were responders and two did not respond to SGLTi therapy.

Few studies have previously addressed the impact of SGLT2i use in the context of myeloid malignancies (Table 2). In a 2023 meeting abstract, Gangat *et al.*[7] reported the impact of SGLT2i use on Hgb and Hct levels in 28 patients with underlying MPN, including polycythemia vera (PV; N=9), essential thrombocythemia (ET; N=11) and myelofibrosis (MF; N=8). Median Hgb levels at baseline and peak for PV, ET and MF patients were 14.1 g/dL and 15.4 g/dL, 12.8 g/dL and 14.5 g/dL, 10.6 g/dL and 11.5 g/dL, respectively. The median Hgb level change in ET patients was 1.5 g/dL (range, 1-4) and in MF patients was 1.6 g/dL (range, 0.7-3.8). There was no correlation between the Hgb changes and *JAK2* variant allele frequency (VAF) or EPO level. In another study, Patir *et al*. reported on Hgb and Hct changes among 16 patients with MPN receiving SGLT2i therapy for other indications, including 14 with ET and two with PV.[8] Median Hgb/Hct levels at baseline and peak were 13.5 g/dL/40.9% and 14.2 g/dL/42.6%, respectively. Six patients needed an additional therapeutic intervention in the form of starting phlebotomy or initiating or adjusting hydroxyurea dose. However, no statistically significant difference was detected between Hgb (P=0.637) or Hct (P=0.367) values before and after SGLT-2 inhibitor initiation.[8] In yet another study of nine consecutive cases of occult MPN, treatment initiation with SGLT2i led to unmasking of overt MPN;[5] in the particular study, baseline median for Hgb/Hct prior to SGLT2i was 15.6 g/dL (range, 14.1-16.3 g/dL)/47.1% (range, 43.1-48.3%). After median duration of 15 months of SGLT2i therapy, all nine patients had significant increase in their Hgb/Hct levels, which led to formal MPN diagnosis: median Hgb/Hct at time of MPN diagnosis were 17.5 g/dL (range, 16.2-19 g/dL)/53.1% (range, 51.1-60%) with median increase from baseline Hgb/Hct of 2.3 g/dL (range, 0.4-3.2 g/dL)/7.4% (range, 3.2-12.7%). Similarly, Das *et al*.[9] reported a patient who had *JAK2* positive PV that was "unmasked" after starting canagliflozin. The

Table 1. Clinical and laboratory characteristics of 11 patients with myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative neoplasm treated with sodium-glucose co-transporter-2 inhibitors.

Variables	N=11
Age in years, median (range)	77 (63-85)
Male sex, N (%)	8 (72)
Leukocyte count x10^9/L, median (range)	6.8 (2.9-10)
Platelet count x10^9/L, median (range)	233 (109-668)
Karyotype, N (%)	
Normal	8 (72)
del(5q)	1 (9)
del(20q)	1 (9)
del(11q) with t(1;4)	1 (9)
Mutations frequencies, N (%)	
SF3B1	7 (63)
U2AF1	2 (18)
ASXL1	2 (18)
CBL	1 (9)
SF3B1	1 (9)
CUX1	1 (9)
PPM1D	1 (9)
SRSF2	1 (9)
TET2	1 (9)
Underlying myeloid disorder*, N (%)	
MDS-*SF3B1*	5 (45)
MDS-MLD	2 (18)
MDS/MPN with *SF3B1* and thrombocytosis	2 (18)
CMML	1 (9)
MDS-del(5q)	1 (9)
SGLT2i dose, N (%)	
Empagliflozin 10 mg	9 (81)
Dapagliflozin 10 mg	2 (18)
Hgb g/dL/Hct% level in non-transfusion-dependent patients, median (range)	
Baseline	9.6/29.9 (8.5-11.2/25.3-35.3)
Peak	10.8/32.7 (10.4-12.4/31.3-38.5)
Last follow-up	10.4/32.05 (7.6-12.4/24.8-37.8)
Baseline to peak change	1.2/3.7 (0-2.2/0.7-7.4)
Baseline to last follow-up change	0.7/2.1 (-2 to 1.3/-4.6 to 5.1)
SGLT2i treatment duration in months, median (range)	9.5 (3-23)

*Based on International Consensus Classification of Myeloid Neoplasms and Acute Leukemias criteria. MDS: myelodysplastic syndrome; MDS/MPN: myelodysplastic syndrome/myeloproliferative neoplasm; MDS-MLD: myelodysplastic syndrome with multilineage dysplasia; CMML: chronic myelomonocytic leukemia; SGLT2i: sodium-glucose co-transporter-2 inhibitors; Hgb: hemoglobin; Hct: hematocrit.



*Patient #8 has been on Darbepoetin α for 3 years prior to starting SGLT2i.
*Patient #3 has been on Luspatercept for 3 months prior to starting SGLT2i.
*Patient #1 has been on Darbepoetin α for 9 months prior to starting SGLT2i.

Figure 1. Hemoglobin levels at baseline, peak and last follow-up with duration of treatment for 11 patients with myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative neoplasm treated with sodium-glucose co-transporter-2 inhibitors.
MDS: myelodysplastic syndrome; MPN: myeloproliferative neoplasm; SGLT2i: sodium-glucose co-transporter-2 inhibitors.

Table 2. Studies reported hemoglobin and hematocrit level changes after sodium-glucose co-transporter-2 inhibitors initiation in patients with underlying myeloid malignancies.

Study	Number of patients and underlying disease	Median (range) baseline Hgb g/dL/Hct%	Median (range) peak Hgb g/dL/Hct%	Median (range) Hgb g/dL/Hct% change
Gangat *et al.*[7]	11 ET	12.8 (9.5-14.9)/38.9 (30.3-44.6)	14.5 (11-16.4)/44.4 (34.8- 51.1)	1.5 (1-4)/5.1 (2.6-13.8)
	9 PV	14.1 (10.5-15.9)/42.7 (33.3-49.2)	15.4 (11.2-19.9)/46.7 (35.9-63.3)	Not reported
	8 MF	10.6 (8.2-14.7)/27.5 (33.8-45.9)	11.5 (10.2-16.1)/35.3 (31.8-49.8)	1.6 (0.7-3.8)/4.3 (1-7.5)
Patir *et al.*[8]	16 total (14 ET and 2 PV)	13.5 (10.8-16.7)/40.9 (34.3-50.1)	14.2 (11.3-16.7)/42.6 (33.3-51.5)	Not reported
Gangat *et al.*[5]	9 total (5 PV, 2 evolving MPN, 1 MPN-U, 1 no bone marrow biopsy done)	15.6 (14.1-16.3)/47.1 (43.1-48.3)	17.5 (16.2-19)/53.1 (51.1-60)	2.3 (0.4-3.2)/7.4 (3.2-12.7)
Das *et al.*[9]	1 PV	14.5/48	16.9/55	2.4/7

Hgb: hemoglobin; Hct%: percentage hematocrit; ET: essential thrombocythemia; PV: polycythemia vera; MF: myelofibrosis; MPN: myeloproliferative neoplasm; MPN-U: myeloproliferative neoplasm-unclassifiable.

patient had Hgb level of 14.5 g/dL at baseline that increased to 16.9 g/dL after 6 months of starting canagliflozin. *JAK2* testing was positive on further evaluation.

Anemia in myeloid neoplasms is multifactorial with putative mechanisms that include ineffective erythropoiesis, defects in iron homeostasis, and dysregulated inflammatory cytokine expression.[10] In MDS and related chronic myeloid neoplasms, some of these mechanisms might be related to increased hepcidin levels. SGLT2i treatment has previously been associated with a significant reduction of hepcidin levels in clinical trials.[11] Accordingly, part of the mechanism involved in the erythropoietic effect of SGLT2i

in MDS might be related to the drug-induced suppression of hepcidin. Another potential mechanism of action might involve the hypoxia-inducible factor (HIF)/prolyl hydroxylase (PH) signaling pathway.[12,13] It is currently assumed that treatment with SGLT2i results in enhanced activation of HIF by mechanisms that include reduced renal tissue oxygen delivery, subsequently leading to increased production of renal erythropoietin.[14] The current study suffers from a number of limitations including small sample size, retrospective design, and lack of a control group. As such, additional larger, prospective, and controlled studies are needed to examine the therapeutic potential of SGLT2i in MDS-associated anemia, either as a single agent or in combination with other anemia drugs, including erythropoiesis-stimulating agents and luspatercept.

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https://doi.org/10.3324/haematol.2024.287032

Received: November 26, 2024.
Accepted: January 13, 2025.
Early view: January 23, 2025.

Disclosures

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

Contributions

AA, SF, FA, NG and AT designed the study and collected data. AA and AT performed the analyses and wrote the paper. All authors reviewed the final draft of the paper.

Data-sharing statement

Please email the corresponding author.

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