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

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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.

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Sodium-glucose co-transporter-2 inhibitors (SGLT2is; 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 changes were $4.8\pm 5.5\%$ and $5.0\pm 5.3\%$ in the groups receiving empagliflozin 10 mg and 25 mg, respectively, compared to $0.9\pm 4.7\%$ in the placebo group¹. 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 hematocrit of 2.67% (95% confidence interval 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 occult⁵ or overt⁶ 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 4 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 2 were transfusion-dependent prior to starting treatment with SGLT2i. Hemoglobin (Hgb) and hematocrits (HCT) levels were

recorded at three time points: (i) at baseline which is the time of SGLT2i treatment initiation, (ii) 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 5 patients, MDS with multilineage dysplasia in 2, MDS/MPN-*SF3B1* and thrombocytosis in 2, chronic myelomonocytic leukemia (CMML) in one, and MDS-del(5q) in one. Six (54%) patients were treatment-naïve prior to SGLT2i initiation, 4 were on active chronic MDS-directed therapy, and one had 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 5 with very low risk disease, 5 low risk and 1 moderate low risk; three patients had therapy related disease. The median (range) values, at the time of SGLT2i treatment start, for leukocyte and platelet counts were $6.8 \times 10^9/L$ (2.9-10) and $233 \times 10^9/L$ (109-668), respectively; karyotype was normal in 8 (72%) patients while next generation sequencing revealed *SF3B1* mutation in 7 (63%), *U2AF1* in 2 (18%), and *ASXL1* in another 2 (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 2 patients who were transfusion-dependent responded. Among the remaining 9 patients who were non-transfusion dependent, median (range) hemoglobin/hematocrit levels at baseline (start of SGLT2i therapy), peak (highest level during SGLT2i therapy), and last follow-up were 9.6 g/dL/29.9% (8.5-11.2/25.3-35.3), 10.8 g/dL/32.7% (10.4-12.4/31.3-38.5) and 10.4 g/dL/32.05% (7.6-12.4/24.8-37.8), respectively (Table 1). Among the 9 non-transfusion dependent patients, 6 (67%) had an increase in hemoglobin level of ≥ 1 g/dL, including 3 (33%) with an increase of ≥ 1.5 g/dL and 2 (22%) ≥ 2 g/dL (Figure 1). Among the 6 responders, 4 (67%) were treatment naïve at the time of SGLT2i therapy initiation. Four (67%) of the 6 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 hemoglobin, among all 9 non-transfusion-dependent patients, was 5 months (range; 1-18); median (range) change in hemoglobin/hematocrit levels from baseline to peak was 1.2 g/dL/3.7% (0-2.2/0.7-7.4) and from baseline to last follow-up was 0.7g/dL/2.1% (-2-1.3/-4.6-5.1). 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 773 x 10⁹/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 5 of the 11 study patients, all of whom were transfusion-independent; timing of testing was 4 months prior to SGLT2i treatment initiation in 2 patients (patients 9 and 10 in figure 1), 3 months before (patient 6), 2 months before (one patient), and 1 week before (one patient); median Epo level was 22.3 mIU/mL (range 14.6-62.2); of these 5 informative cases, 3 were responders and 2 did not respond to SGLT2i 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 al⁷ reported the impact of SGLT2i use on hemoglobin and hematocrit levels in 28 patients with underlying MPN, including polycythemia vera (PV; n=9), essential thrombocythemia (ET; n=11) and myelofibrosis (MF; n=8). Median hemoglobin 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 (range) hemoglobin level change in ET patients was 1.5 g/dL (1-4) and in MF patients was 1.6 g/dL (0.7-3.8). There was no correlation between the hemoglobin changes and *JAK2* variant allele frequency (VAF) or erythropoietin (EPO) level. In another study, Patir et al. reported on hemoglobin and hematocrit changes among 16 patients with MPN receiving SGLT2i therapy for other indications, including 14 with ET and 2 with PV⁸. Median hemoglobin/hematocrit 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 initiation⁸. In yet

another study of 9 consecutive cases of occult MPN, treatment initiation with SGLT2i led to unmasking of overt MPN⁵; in the particular study, baseline median (range) for Hgb/Hct prior to SGLT2i was 15.6 g/dL(14.1–16.3 g/dL)/47.1% (43.1%–48.3%). After median duration of 15 months of SGLT2i therapy, all 9 patients had significant increase in their Hgb/Hct levels, which led to formal MPN diagnosis: median (range) Hgb/Hct at time of MPN diagnosis were 17.5 g/dL (16.2–19 g/dL)/53.1% (51.1%–60%) with median increase from baseline Hgb/Hct of 2.3 g/dL (0.4–3.2 g/dL)/7.4% (3.2%–12.7%). Similarly, Das et al⁹ reported a patient who had *JAK2* positive PV that was “unmasked” after starting Canagliflozin. The patient had hemoglobin 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 expression¹⁰. 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 trials¹¹. 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 HIFs by mechanisms that include reduced renal tissue oxygen delivery, subsequently leading to increased production of renal erythropoietin¹⁴. 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.

References

1. 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.
2. Wang X, Fu R, Liu H, Ma Y, Qiu X, Dong Z. The effects of sodium glucose co-transporter (SGLT) 2 inhibitors on hematocrit levels: a systematic review and meta-analysis of randomized controlled trials. *Ann Palliat Med*. 2021;10(6):6467-6481.
3. Gangat N, Szuber N, Alkhateeb H, Al-Kali A, Pardanani A, Tefferi A. JAK2 wild-type erythrocytosis associated with sodium-glucose cotransporter 2 inhibitor therapy. *Blood*. 2021;138(26):2886-2889.
4. 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.
5. Gangat N, Alkhateeb H, Reichard K, Tefferi A. Sodium-glucose co-transporter-2 inhibitor therapy and unmasking of -mutated myeloproliferative neoplasm: A Mayo Clinic series of nine consecutive cases. *Am J Hematol*. 2023;98(10):E276-E280.
6. 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.
7. Gangat N, Karrar O, Abdelmagid M, et al. Sodium-Glucose Co-Transporter-2 Inhibitor Use in the Setting of Myeloproliferative Neoplasms: Impact on Hemoglobin/Hematocrit Levels and Thrombosis Risk. *Blood*. 2023;142(Supplement 1):1815.
8. Patir P, Cerci K, Kurtoglu E. Myeloproliferative Neoplasms and Sodium-Glucose Co-Transporter-2 Inhibitors: A Case Series. *Turk J Haematol*. 2024;41(2):130-132.
9. Das L, Bhansali A, Walia R. Unmasking and aggravation of polycythemia vera by canagliflozin. *Diabet Med*. 2018;35(11):1613-1616.
10. Tefferi A. New drugs for myeloid neoplasms with ring sideroblasts: Luspatercept vs imetelstat. *Am J Hematol*. 2021;96(7):761-763.
11. Docherty KF, Welsh P, Verma S, et al. Iron Deficiency in Heart Failure and Effect of Dapagliflozin: Findings From DAPA-HF. *Circulation*. 2022;146(13):980-994.
12. Luo Z, Tian M, Yang G, et al. Hypoxia signaling in human health and diseases: implications and prospects for therapeutics. *Signal Transduct Target Ther*. 2022;7(1):218.
13. Gangat N, Tefferi A. Targeting anemia in myeloid neoplasms. *Am J Hematol*. 2024;99(9):1663-1666.
14. 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.

Table 1: Clinical and laboratory characteristics of 11 patients with myelodysplastic syndrome or myelodysplastic syndrome/myeloproliferative neoplasm (MDS or MDS/MPN) treated with of sodium–glucose co-transporter-2 inhibitors (SGLT2i).

| Variables | n=11 |
|--|------------------------------------|
| Age in years, median (range) | 77 (63-85) |
| Male gender, n (%) | 8 (72) |
| Leukocyte count x 10 ⁹ /L, median (range) | 6.8 (2.9-10) |
| Platelet count x 10 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 (%) | |
| <i>SF3B1</i> | 7 (63) |
| <i>U2AF1</i> | 2 (18) |
| <i>ASXL1</i> | 2 (18) |
| <i>CBL</i> | 1 (9) |
| <i>SF3B1</i> | 1 (9) |
| <i>CUX1</i> | 1 (9) |
| <i>PPM1D</i> | 1 (9) |
| <i>SRSF2</i> | 1 (9) |
| <i>TET2</i> | 1 (9) |
| Underlying myeloid disorder*, n (%) | |
| MDS- <i>SF3B1</i> | 5 (45) |
| MDS-MLD | 2 (18) |
| MDS/MPN with <i>SF3B1</i> 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) |
| Hemoglobin and hematocrit level g/dl/%, median (range) in non-transfusion dependent patients | |
| 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 (-2-1.3/-4.6-5.1) |
| 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.

Table 2: Studies reported hemoglobin and hematocrit level changes after sodium–glucose co-transporter-2 inhibitors (SGLT2i) initiation in patients with underlying myeloid malignancies.

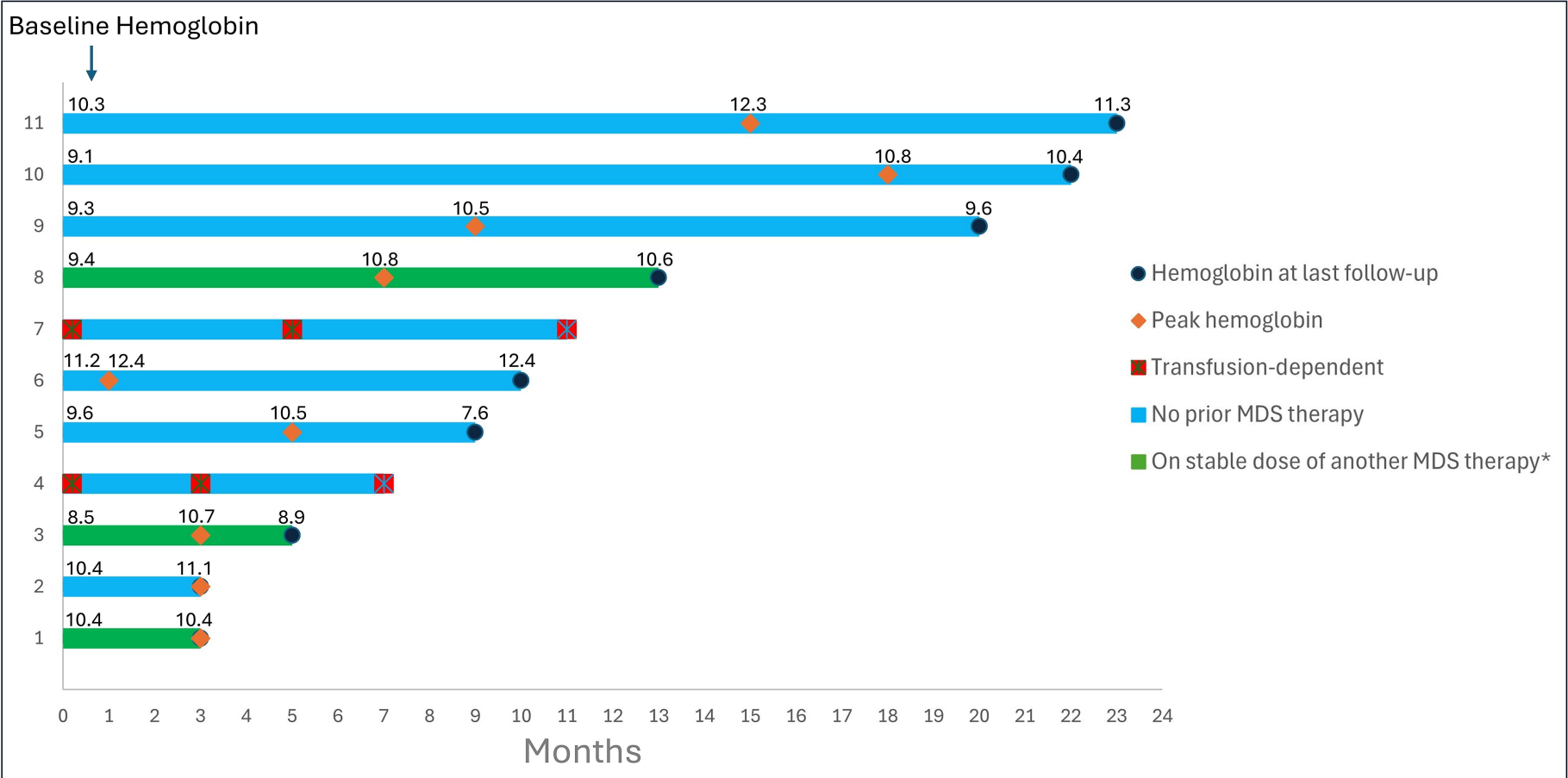
| Study | Number of patients and underlying disease | Median (range) baseline Hgb g/dL/Hct% | Median (range) peak Hgb g/dL/Hct% | Median (range) Hgb g/dL/Hct% change |
|---------------------------|---|---------------------------------------|-----------------------------------|-------------------------------------|
| 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 |

ET: essential thrombocythemia, PV: polycythemia vera, MF: myelofibrosis, MPN: myeloproliferative neoplasm, MPN-U: myeloproliferative neoplasm-unclassifiable.

Figure Legend

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 (MDS or MDS/MPN) treated with sodium–glucose co-transporter-2 inhibitors (SGLT2i).

Figure 1:



*Patient #8 has been on Darbepoetin alfa 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 alfa for 9 months prior to starting SGLT2i.