LETTER TO THE EDITOR

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# Myeloproliferative Neoplasms and Sodium-Glucose Co-Transporter-2 Inhibitors: A Case Series

## Miyeloproliferatif Neoplaziler ve Sodyum-Glukoz Ko-Transporter-2 İnhibitörleri: Bir Olgu Serisi

Püsem Patır[1], Kübra Çerçi[2], Erdal Kurtoğlu[1]

[1]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Hematology, Antalya, Türkiye
[2]University of Health Sciences Türkiye, Antalya Training and Research Hospital, Department of Internal Medicine, Antalya, Türkiye

**To the Editor,**

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors constitute a group of drugs that act independently of the effect of insulin, provide weight loss with a decrease in blood sugar levels by inhibiting renal glucose reabsorption, and are used in the treatment of type 2 diabetes mellitus (DM) [1]. SGLT-2 inhibitors have been shown to provide significant additional clinical benefits besides glycemic control in patients with heart failure and diabetic nephropathy [2]. However, the mechanisms underlying these benefits remain unclear. SGLT-2 inhibitors significantly increase hemoglobin (Hgb) and hematocrit (Hct) levels, which serve as markers of cardiorenal protection [3]. The use and prescription of SGLT-2 inhibitors are likely to increase with the emergence of their cardiorenal protection and regeneration properties in addition to glycemic control. We aimed to clarify this issue by examining treatment strategies and subsequent thrombotic events among patients with myeloproliferative neoplasms (MPNs) using SGLT-2 inhibitors.

A total of 436 adult MPN patients (250 patients with essential thrombocythemia, 142 with polycythemia vera, and 44 with myelofibrosis) diagnosed between 2015 and 2022 in our clinic were analyzed retrospectively. Among 98 patients with a concurrent diagnosis of DM (53 patients with essential thrombocythemia, 33 with polycythemia vera, and 12 with myelofibrosis), 16 patients (median age: 61 years; range: 42-74 years; 56% women) using SGLT-2 inhibitors were evaluated. The characteristics of the MPN patients using SGLT-2 inhibitors are detailed in Table 1. These patients received SGLT-2 inhibitor therapy for a median of 17.8 months (range: 0.9-54.1 months). The median values and ranges for baseline Hgb and Hct levels before the initiation of SGLT-2 inhibitors were 13.5 g/dL (10.8-16.7 g/dL) and 40.9% (34.3%-50.1%), while they were 14.2 g/dL (11.3-16.7 g/dL) and 42.6% (33.3%-51.5%) after the initiation of SGLT-2 inhibitors, respectively. No significant difference was detected between Hgb (p=0.637) or Hct (p=0.367) values before and after SGLT-2 inhibitor initiation. The MPN treatments of 6 patients were changed after starting the SGLT-2 inhibitors. The hydroxyurea dose was increased for two patients, the hydroxyurea dose was increased and phlebotomy was performed for two patients, phlebotomy alone was performed for one patient, and hydroxyurea was started and phlebotomy was performed for one patient. No new thrombosis occurred with the administration of the SGLT-2 inhibitors. Additionally, this potential side effect was not fully considered when starting SGLT-2 inhibitors for the patients with polycythemia vera. No difference was observed in the Hgb and Hct values of one of the two polycythemia vera patients using SGLT-2 inhibitors. The other polycythemia vera patient could not be evaluated because she was lost to follow-up.

The present case series is the first report on the use of SGLT-2 inhibitors in patients with MPN. Das et al. [4] presented a patient who used an SGLT-2 inhibitor (canagliflozin) and was diagnosed with *JAK2*V617F-positive polycythemia vera due to increases in Hgb and Hct during follow-up. Gangat et al. [5,6] evaluated 100 patients with SGLT-2 inhibitor-related *JAK2*-unmutated erythrocytosis. They found that thrombotic risk was independent of high Hct and was higher in those who underwent phlebotomy. In this context, they emphasized that phlebotomy has limited therapeutic value. Considering the beneficial effects of SGLT-2 inhibitors, they recommended that treatment not be discontinued early for erythrocytosis.

In conclusion, it is important to monitor Hct because increased Hct may predispose to arterial thrombotic events such as myocardial infarction and stroke [7]. This case series emphasizes that close Hgb and Hct monitoring could be important during the use of SGLT-2 inhibitors by patients diagnosed with MPNs.

**Table 1. Characteristics of patients with myeloproliferative neoplasms using SGLT-2 inhibitors.**

| Age/ sex | Diagnosis | Mutation | Comorbidity | IPSET for ET [8] IPSS for PV [9] | Treatment | SGLT-2 inhibitor type | Intervention in MPN treatment | Thrombosis after SGLT-2 |
|---|---|---|---|---|---|---|---|---|
| 64/F | ET | *JAK2* | HTN, HLD | High | HU + ASA | Empagliflozin | No | No |
| 61/F | ET | Triple-negative | HLD | Low | HU + ASA | Empagliflozin | Yes | No |
| 59/F | ET | *JAK2* | HTN, HLD, CVD | Intermediate | HU + ASA + clopidogrel | Empagliflozin | Yes | No |
| 69/M | ET | *JAK2* | HTN, HLD, CAD, CHF | High | HU + ASA + warfarin | Empagliflozin | Yes | No |
| 53/F | ET | Triple-negative | Asthma | Low | ASA | Dapagliflozin | Yes | No |
| 59/M | ET | *JAK2* | HTN | Intermediate | HU + ASA | Empagliflozin | No | No |
| 45/M | ET | *JAK2* | HLD | Intermediate | Anagrelide + ASA | Empagliflozin | NR | No |
| 63/M | ET | *JAK2* | HTN, HLD, CAD | Intermediate | HU + ASA | Empagliflozin | Yes | No |
| 50/F | ET | Triple-negative | HTN, HLD | Low | ASA | Dapagliflozin | No | No |
| 40/F | ET | *CALR* | HLD | Intermediate | ASA | Empagliflozin | Yes | No |
| 66/F | ET | *JAK2* | HTN, HLD | High | HU + ASA | Dapagliflozin | No | No |
| 57/F | ET | *JAK2* | HTN, HLD, CAD | Intermediate | HU + ASA | Dapagliflozin | No | No |
| 60/M | ET | *JAK2* | HTN, HLD, CAD | Intermediate | HU + ASA | Empagliflozin | No | No |
| 54/M | PV | *JAK2* | HTN, HLD, CAD, CHF | Intermediate | HU + ASA | Empagliflozin | No | No |
| 61/F | PV | *JAK2* | HTN, HLD, CAD | High | HU + ASA | Empagliflozin | NR | No |
| 73/M | ET | *CALR* | HTN, HLD | High | Anagrelide + ASA | Empagliflozin | No | No |

F: Female; M: male; ET: essential thrombocythemia; PV: polycythemia vera; HTN: hypertension; HLD: hyperlipidemia; CVD: cerebrovascular disease; CAD: coronary artery disease; CHF: congestive heart failure; IPSET: International Prognostic Score for Essential Thrombocythemia; IPSS: International Prognostic Scoring System; HU: hydroxyurea; ASA: acetylsalicylic acid; MPN: myeloproliferative neoplasm; NR: not reported.

A dose increase in treatment and/or phlebotomy may be needed during follow-up, but it would be appropriate to take individualized approaches until more data are obtained.

**Keywords:** Myeloproliferative neoplasms, Gliflozins, Thrombosis

**Anahtar sözcükler:** Myeloproliferatif neoplaziler, Gliflozinler, Tromboz

### Ethics

**Informed Consent:** Informed consent was obtained from the patients for publication.

### Authorship Contributions

Concept: P.P., K.Ç., E.K.; Design: P.P., K.Ç., E.K.; Data Collection or Processing: P.P., K.Ç.; Analysis or Interpretation: P.P., E.K.; Literature Search: P.P.; Writing: P.P.

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**Address for Correspondence/Yazışma Adresi:** Püsem Patır, M.D., University of Health Sciences Türkiye, Antalya Training and Research Hospital, Clinic of Hematology, Antalya, Türkiye
**Phone :** +90 242 249 44 00
**E-mail :** pusemp@yahoo.com ORCID: orcid.org/0000-0001-5201-4680

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