LETTERS TO THE EDITOR

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

Pusem Patir[1], Kubra Cerci[2], Erdal Kurtoglu[1]
[1] University of Health Sciences, Antalya Training and Research Hospital, Department of Hematology, Antalya, Turkey
[2] University of Health Sciences, Antalya Training and Research Hospital, Department of Internal Medicine, Antalya, Turkey

Pusem Patir M.D., University of Health Sciences, Antalya Training and Research Hospital, Department of Hematology, Antalya, Turkey
pusemp@yahoo.com

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To the Editor,

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

Four hundred and thirty-six adult CMN patients (250 patients had essential thrombocythemia, 142 had polycythemia vera, and 44 had myelofibrosis) diagnosed between 2015 and 2022 in our clinic were analyzed retrospectively. Among 98 patients (53 patients had essential thrombocythemia, 33 had polycythemia vera, and 12 had myelofibrosis) with a concurrent diagnosis of DM, 16 patients (median age, 61 years; range, 42-74; 56% females) using SGLT-2 inhibitors were evaluated. Characteristics of CMN patients using SGLT-2 inhibitors are detailed in Table 1. Patients received SGLT-2 inhibitor therapy for a median of 17.8 months (range, 0.9-54.1 months). Median and range for baseline Hgb/Hct levels before and after initiation of SGLT-2 inhibitors were 13.5 g/dL (10.8-16.7 g/dL)/40.9% (34.3%-50.1%) and 14.2 g/dL (11.3-16.7 g/dL)/42.6% (33.3%-51.5%), respectively. No significant difference was detected between Hgb ($p = 0.637$) and Hct ($p = 0.367$) values before and after SGLT-2 inhibitor. CMN treatment of 6 patients was intervened after starting SGLT-2 inhibitor. The hydroxyurea dose was increased in two patients, the hydroxyurea dose was increased and phleobotomy was performed in two patients, only phleobotomy was performed in one patient, the hydroxyurea was started and phleobotomy was performed in one patient. No new thrombosis occurred under SGLT-2 inhibitor. Additionally, this potential side effect has not been fully considered when starting SGLT-2 inhibitors in PV patients. With this, no difference was observed in Hgb/Hct values in one out of two PV patients using SGLT-2 inhibitors. The other PV 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 CMN. Das et al. presented a case who used SGLT2 inhibitor (canagliflozin) was diagnosed with JAK2V617F positive PV due to the increase in Hgb/Hct during follow-up [4]. Gangat et al. evaluated 100 patients with SGLT-2 inhibitor related JAK2 unmutated erythrocytosis [5,6]. 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.

As a result, 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/Hct monitoring could be important during the use of SGLT-2 inhibitors in patients diagnosed with CMN. A dose increase in treatment and/or phlebotomy may be needed during follow-up, but it would be appropriate to take an individualized approach until more data is obtained.

Keywords: Myeloproliferative neoplasias, gliflozins, thrombosis
Anahtar sözcükler: Myeloproliferatif neoplaziler, gliflozinler, tromboz

Ethics
The study was approved by the Local Ethics Committee of the University of Health Sciences … Training and Research Hospital (24/08/2023–11/4). This study was conducted in accordance with the 1964 Helsinki Declaration.

Authorship Contributions
All authors contributed to both the conception and design of this study. Medical Practices: … ; Data Collection or Processing: … ; Analysis or Interpretation: ... ; Literature Search: ... ; Writing: …

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Table 1. Characteristics of CMPN patients using SGLT-2 inhibitors

Age/Sex	Diagnosis	Mutation	Comorbidity	IPSET for ET[8] IPSS for PV[9]	Treatment	SGLT-2 Inhibitor Type	Intervention in CMPN Treatment	Thrombosis after SGLT-2
64/F	ET	JAK2	HTN,HLD	High	HU+ASA	Empagliflozn	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	Intermedaite	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

ET, Essential thrombocythemia; PV, Polycythemia vera; HTN, Hypertension; HLD, Hyperlipidemia; CVD, Cerebrovascular disease; CAD, Coronary artery disease; CHF, congestive heart failure; HU, Hydroxyurea; ASA, Acetylsalicylic acid; NR, Not reported.