The efficacy and safety of sodium-glucose cotransporter inhibitors in cancer patients with heart failure: A single-center experience

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INTRODUCTION

Current guidelines recommend sodium-glucose cotransporter (SGLT2) inhibitors for patients with heart failure (HF) and reduced left ventricular ejection fraction (LVEF), recently also with preserved and mildly reduced LVEF [1]. This relatively new class of initial antidiabetic drugs demonstrated significant cardiovascular (CV) and renal benefits regardless of the presence of diabetes. Recently, in pilot studies, they have also been recognized as agents that have a potential anticancer effect [2]. However, there is a lack of evidence on the efficacy and safety of flozins in HF patients with cancer. The cancer population frequently shares many CV risk factors with cardiac diseases. Cancer patients may suffer from HF of origin similar to the general population or HF may be a consequence of CV toxicity related to cancer therapy. Treatment of HF in cancer patients, especially during ongoing oncologic therapy, is challenging. These patients are particularly vulnerable to electrolyte imbalance, kidney function deterioration, dehydration, and changes in blood pressure (BP). Against this background, our objective was to conduct a prospective single-center study investigating the effectiveness and safety of SGLT2 inhibitors in cancer patients with HF.

METHODS

Cancer patients treated at the Subcarpathian Oncological Centre of the University Clinical Hospital in Rzeszow between 2022 and 2023 with concomitant stable HF were included in the study. Patients received the SGLT2 inhibitor as part of standard HF therapy according to the recommendations for the general population [1]. Exclusion criteria were significant renal failure (for safety reasons, as patients at the same time started systemic therapy, SGLT2-inhibitors were not initiated in patients with a glomerular filtration rate [eGFR] below 45 mL/min/1.73 m^2; in the general population, the limit values of eGFR are 25 for dapagliflozin and 20 for empagliflozin), genitourinary infections, and a high risk of dehydration. The study was approved by the local Bioethics Committee (approval number 89/2022/B), and all patients gave their informed consent to participate in the study. Demographic and clinical characteristics were obtained. Physical examination, orthostatic BP measurements (for orthostatic hypotension screening), New York Heart Association (NYHA) class assessment, laboratory data including N-terminal pro B-type natriuretic peptide (NT-proBNP), potassium and sodium levels, eGFR, and echocardiography with LVEF assessment were obtained at baseline and 3 months after SGLT2 inhibitor treatment.

Statistical analysis

Data were presented as median, lower, and upper quartiles for quantitative variables and as percentages for qualitative variables. The Wilcoxon signed rank test and the McNemar exact test for paired dichotomous data were used for comparison. All analyses were performed in STATISTICA 13 (StatSoft). *P*-values <0.05 were considered statistically significant.

RESULTS AND DISCUSSION

Thirty patients were included at a median age of 69, and 37% were female. Among these patients, 87% had hypertension, 57% diabe-

Table 1. Clinical, biochemical, and echocardiographic measurements of patients before and after 3-month SGLT2 inhibitor treatment according to HF etiology

	CTRCD (n = 9)			Other HF (n = 21)			All (n = 30)		
	Before SGLT2i	After SGLTi2	*P*-value	Before SGLTi2	After SGLTi2	*P*-value	Before SGLTi2	After SGLTi2	*P*-value
NYHA functional class, n (%) I+II	3 (33.3)	9 (100.0)	0.15	7 (33.3)	20 (95.2)	0.08	10 (33.3)	29 (96.7)	0.02
NYHA functional class, n (%) III+IV	6 (66.7)	0 (0.0)		14 (66.7)	1 (4.8)		20 (66.7)	1 (3.3)	
Orthostatic hypotension, n (%)	4 (44.4)	3 (33.3)	0.75	8 (38.1)	10 (47.6)	0.65	12 (40.0)	13 (43.3)	0.46
NT-proBNP, pg/ml	1298.0 (1190–1890)	983.0 (874–1041)	0.01	1372.5 (728.5–1967)	876.0 (572–1237)	<0.001	1298.0 (834–1890)	925.5 (578–1237)	<0.001
Sodium level, mmol/l	137.0 (135–138)	135.0 (135–136)	0.72	139.5 (136–142)	140.0 (135–141.5)	0.65	138.0 (136–141)	139.0 (135–140)	0.85
Potassium level, mmol/l	3.9 (3.9–4.4)	4.4 (4.2–4.7)	0.14	4.4 (3.9–4.7)	4.3 (4.0–4.6)	0.91	4.2 (3.9–4.7)	4.3 (4.1–4.7)	0.48
Estimated glomerular filtration rate, ml/min/1.73 m^2	66.0 (64–67)	65.0 (65–66)	0.44	62.0 (56–66)	62.0 (55–65)	0.41	64.0 (56–66)	64.5 (55–65)	0.76
Left ventricular ejection fraction %	43.0 (40–47)	48.0 (48–54)	0.01	40.0 (30–48)	48.0 (35–51)	<0.001	40.0 (35–47)	48.0 (42–51)	<0.001

Data are presented as medians with lower and upper quartiles (in brackets) or as percentages

Abbreviations: BP, blood pressure; CTRCD, cancer therapy-related cardiac dysfunction; HF, heart failure; NT-proBNP, N-terminal pro B-type natriuretic peptide; NYHA, New York Heart Association; SGLT2i, sodium-glucose cotransporter inhibitor

tes, 77% dyslipidemia, 77% were active or past smokers, and 30% had obesity. At least three CV risk factors were present in 47% of the patients. There were 16 HF patients with reduced LVEF, 8 patients with mildly reduced LVEF, and 6 patients with preserved LVEF. In 9 patients, HF was the result of cardiovascular toxicity related to cancer therapy (in 7 cases due to anthracycline/anti-HER2 therapy; in one due to taxanes, and in one due to antimetabolite therapy). In the remaining cases, HF was not related to cancer treatment but was already present, or newly diagnosed, during routine cardiologic consultation before starting oncology therapy.

The most common cancers were gastrointestinal (n = 10), breast (n = 7), head/neck (n = 4), and others (lung, urinary, and malignant melanoma). All patients were actively treated with various antineoplastic agents; 7 received anthracyclines/anti-HER2 agents, 4 alkylating drugs, 9 antimetabolites, 3 taxanes, 7 immunotherapy, and 4 radiation therapy.

SGLT2 inhibitors were added to standard HF therapy that included 80% beta-blockers, 90% angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, and 37% mineralocorticoid receptor antagonists. Empagliflozin was started in 23 cases and dapagliflozin in 7 in a standard dose of 10 mg once daily. The patients were followed for 3 months. The main results are presented in Table 1.

At the end of the 3-month follow-up, a significant improvement was observed in the functional NYHA class for the whole group, the level of NT-proBNP, and LVEF in each studied group. In general, we observed no significant changes in other laboratory parameters, renal function, or BP values. Implementing SGLT2 inhibitors did not negatively affect the frequency of orthostatic hypotension. During observation, 3 patients discontinued the SGLT2 inhibitor: a male patient due to recurring genitourinary infections, another man due to transient worsening of renal function to eGFR 26 ml/min/1.73 m^2 (not requiring dialysis), and a female patient due to severe skin rash lesions. None of the patients died or experienced acute cardiac events during the follow-up period. We did not observe any differences in the studied parameters between HF induced by oncologic therapy and HF due to other causes.

Based on current knowledge, our study provides the first prospective data on the efficacy and safety of SGLT2 inhibitors in cancer patients with HF. Our observation confirms that SGLT2 inhibitors can be successfully implemented in this population, with a relatively low rate of complications. The implementation of SGLT2 inhibitors resulted in overall significant improvement in NYHA class, cardiac biomarkers, and LVEF in each studied group, with no deterioration in BP control or renal function, and with only a 3% rate of discontinuation.

To date, we have access to results from retrospective analyses on cancer patients who received flozins for diabetes treatment. The study by Gongora et al. [3] in a small group of patients (n = 32) documented that the use of SGLT2 inhibitors is associated with a lower rate of cardiac events among diabetic patients with cancer treated with anthracyclines — agents of widely known potential cardiotoxic effects. Another retrospective study involving diabetic patients in whom SGLT2 inhibitors were introduced before cancer diagnosis and continued afterward documented that SGLT2 use was associated with a reduction in the rate of hospital admissions for HF and improved overall survival [4]. Interestingly, the results of a recently published meta-analysis confirmed also a positive effect of SGLT-2 on carcinogenesis in diabetic patients, showing that flozin use was associated with significantly reduced risk of cancer compared to placebo [5].

Quagliariello et al. [6] showed in mouse models that the use of empagliflozin exerted cardioprotective effects in doxorubicin-induced cardiotoxicity, similar data are

also available in animal models for trastuzumab-induced cardiotoxicity [7]. So far, there are no publications on using SGLT2 inhibitors with HF indication in cancer patients. The presence of cancer is a common exclusion criterion in clinical trials. However, HF frequently accompanies cancer diagnosis due to common CV risk factors, the presence of cancer itself, and the use of oncology therapy that can induce HF. The most common cancers that coexist with CV disease are lung cancers and hematologic malignancies [8]. The prevalence of any cardiovascular disease in lung cancer, according to analysis of US databases, reaches 43% and HF — 12%. Since there are no similar data in Poland, a national registry was established under the auspices of the Polish Cardiac Society to assess the prevalence of cardiovascular diseases and CV risk factors in oncology patients — CONNECT-POL. The registry should also improve the development of cardio-oncology teams in Poland, as currently they are not supported by the public health system.

The optimal HF treatment in cancer patients is critical. The development or deterioration of HF can negatively influence the prognosis of cancer patients or even result in the discontinuation of oncologic treatment. The results of our study are optimistic, showing that the use of SGLT2 inhibitors in cancer patients may be safe and effective in improving their functional status. We have observed beneficial effects of SGLT2 inhibitors in cancer patients with preexisting HF and HF induced by oncology therapy.

The major limitation of the study is the short observation time that did not allow assessment of oncologic and cardiac long-term outcomes. Furthermore, the single-center protocol, small sample size, and the non-homogeneous cancer cohort make the study less reliable compared to multicenter randomized trials. These limitations should be overcome by carefully planned future studies.

Article information

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