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ORIGINAL ARTICLE

Plasminogen Activator Inhibitor-1 and Circulating Ceruloplasmin Levels in Men with Iron-Deficiency Anemia and Heart Failure with Concomitant Prostate Cancer and Their Dynamics after Treatment

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Background: The aim was to determine the activity of plasminogen activator inhibitor-1 (PAI-1) and levels of circulating ceruloplasmin (CP) in men with iron-deficiency (ID) anemia and heart failure with preserved ejection fraction (HFpEF) with concomitant prostate cancer and their dynamics after intravenous iron hydroxide sucrose supplementation. **Methods:** Dynamic observation and treatment was performed in 53 men with ID anemia and HFpEF with concomitant prostate adenocarcinoma. Serum PAI-1 activity levels were determined using a modified colorimetric method of tissue-type plasminogen activator determination. Serum CP levels were evaluated by immunoblot assay. **Results:** After 10 days of treatment in the group of patients treated with intravenous iron (III) hydroxide sucrose, the median PAI-1 activity level decreased by 9.2% ($P < 0.001$), in Group II, this indicator was not significantly different. After 10 days of treatment, it was estimated decreased median CP level by 35% ($P < 0.001$), in comparison with standard therapy – on 14.4% ($P < 0.001$). **Conclusion:** The infusion of intravenous iron (III) hydroxide sucrose in men with ID anemia and HFpEF with concomitant prostate cancer contributed to a significant decrease of PAI-1 activity level and CP level.

Key words: Plasminogen activator inhibitor-1, circulating ceruloplasmin, iron-deficiency anemia, HF with preserved ejection fraction, prostate cancer, intravenous iron supplementation

INTRODUCTION

Heart failure with preserved ejection fraction (HFpEF) represents up to 50% in HF structure and associated with a high level of mortality and comorbidity.[1] HFpEF has recently become important issue, while pharmacological treatment can increase the survival in HF with reduced ejection fraction (HFrEF), no medications show appropriate effectiveness in HFpEF.[2]

In recent years, a cardio-oncology subspecialty has been actively formed due to growing population of cancer survivors and increasing number of patients with induced HF by cancer therapy. The main goal of cardio-oncology is to reduce the burden of cardiovascular diseases in oncologic patients.[3]

Prostate cancer is one of the most common forms of cancer among men.[4] The rate of cardiovascular diseases among prostate cancer cases is growing.[5] Recent studies have demonstrated the association between androgen deprivation therapy with a 72% higher risk of HF in a study of patients with prostate cancer.[6] The European Society of Cardiology (ESC) has issued a 2016 Position Paper on Cancer Treatments and Cardiovascular Toxicity with summarizing the most important recommendations.[7] But currently, there are no recommendations for management patients with prostate cancer, who have preexisting HF or cardiovascular toxicity with developing HF caused by androgen deprivation therapy.

An increasing amount of research has demonstrated the existence of various dysmetabolic disorders in patients

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with prostate adenocarcinoma.[8] Thus, studies have revealed the complexity of the iron metabolism in prostate cancer cells; in fact, cancer cell proliferation is related to the iron phenotype of other cells of the tumor microenvironment.[9,10] The causes of anemia in patients with prostate cancer include androgen deprivation therapy, nutritional disturbance, bone marrow infiltration, treatment-related toxicity, and chronic inflammation.[11] For patients without indications for hemotransfusion, the use of erythropoietin, iron preparations, and vitamin supplementation may be beneficial, but randomized, prospective studies are lacking.[12]

The increased overall and cardiovascular mortality in case of anemia presence in patients with HF was confirmed in a large number of studies.[13] The mechanism of the development of anemia in HF patients is multifactorial.[14] Iron deficiency (ID) is common in patients with HF and is associated with reduced physical tolerance, impaired quality of life, and an increased risk of mortality.[13,15] The numerous randomized controlled clinical trials have demonstrated the effectiveness of intravenous iron to correct ID in patients with HFrEF.[16,17] The 2016 ESC guidelines noted that patients with HF ID should be routinely tested for ID and treated in symptomatic patients with HFrEF and ID (serum ferritin <100 μg/L, or ferritin 100–299 μg/L and transferrin saturation <20%).[18] In addition, further evidence is needed concerning the effect of iron repletion in patients with HFpEF. The American College of Cardiology guidelines do not recommend any specific formulation but, although, recommend intravenous iron in patients with HF and ID.[13]

Ceruloplasmin (CP) is a copper-containing α_2-glycoprotein, which is synthesized in liver and responsible for the transport of circulating copper. CP is also involved in iron metabolism. Thus, CP provides the normal transport of iron from cells to plasma and catalyzes oxidation of ferrous iron (Fe^{2+}).[19] CP is known as an acute-phase protein that may underlie several cardiovascular diseases.[20] Interestingly CP was associated with the inflammatory factors in patients with acute aortic dissection and positioned as potential biomarker for increased risk of thrombosed false lumen.[21]

ID anemia (IDA) is a well-known prothrombotic condition. The searching for the causes of increased thrombotic risk in IDA remains an issue. Plasminogen activator inhibitor-1 (PAI-1) is produced by endothelial cells and suppresses the fibrinolytic process by inhibiting tissue-type plasminogen activator (tPA).[22] In pathologic conditions, PAI-1 production can be upregulated by pro-inflammatory factors and inducts pro-thrombotic state.[23] The assessment of the impact of elevated PAI-1 in HF patients has yet to be evaluated.

Thus, the purpose of the present study was to determine the activity of PAI-1 and levels of circulating CP in men with ID anemia and HFpEF with concomitant prostate cancer and their dynamics after intravenous iron (III) hydroxide sucrose supplementation.

MATERIALS AND METHODS

The present study was conducted with approval from University Institutional Review Board and Local Ethics Committee according to the Helsinki declaration principles (IRB institution name: Dnipro medical academy, approval number: 554/20). All participants of the research gave informed written consent. Dynamic observation and treatment was performed in 53 men with ID anemia and HFpEF with concomitant prostate adenocarcinoma at the age of 45–75 years. The baseline characteristics of patients are demonstrated in Table 1.

All patients had HF according to the classification of the European Society of Cardiology, the diagnosis of prostate cancer was confirmed by a biopsy. During follow-up, all patients received the standard treatment of HF and prostate cancer which did not change during the whole observation period. All patients with prostate cancer were previously undertreated and had stable disease for more than 24 weeks with decreasing of prostate-specific antigen level.

The inclusion criteria were men aged 45–75 years, the presence of a verified diagnosis of prostate cancer, consistently selected anticancer therapy for 6 months, the presence of a verified diagnosis of HF 2–3 grade functional class (FC) (New York Heart Association [NYHA]) with EF >40% on the coronary artery disease background, anemia with hemoglobin (Hb) level of 90–130 g/l and ferritin level <100 mg/ml; consistently selected cardiologic treatment for the last 3 months, and voluntary informed consent to participate in the study.

Exclusion criteria from the study considered age over 75 years, anemia due to other factors (blood loss from the gastrointestinal tract, gynecological pathology), active gastric or duodenal ulcer, anemia with Hb <80 g/l, thrombocytopenia, the presence of HF with EF <40%; arrhythmias, acute MI, acute cerebrovascular accident, diabetes, hyper- and hypothyroidism with transglutaminase levels >10 mU/l, chronic kidney insufficiency (glomerular filtration rate [GFR] <30 ml/min./1.73 m^2), acute HF, obesity with grade 4, and cachexia.

Patients were blindly divided into two groups: Group I (n = 28) – patients with ID anemia on the HFpEF and prostate cancer treated with intravenous iron (III) hydroxide sucrose (Sufer, Yuria Farm) intravenously during 10 days in addition to standard therapy. The dose was calculated individually, in accordance with the general ID according

Table 1: Baseline characteristics of the study patients

Characteristic	Main group (patients with iron -deficiency anemia and heart failure with preserved ejection fraction and prostate cancer, *n*=53)	Comparison Group 1 (patients with heart failure with preserved ejection fraction and prostate cancer without iron -deficiency anemia, *n*=21)	Comparison Group 2 (patients with heart failure with preserved ejection fraction and iron -deficiency anemia without prostate cancer, *n*=20)
Median of age (years)	66 (57.5; 74.4)	65.7 (58.7; 72.3)	66.5 (58.9; 73.5)
Median duration of HF (years)	9.8 (7.3; 10.8)	9.1 (7.1; 9.8)	9.3 (7.8; 10.3)
GFR, ml/(min 1.73 m^2)	74 (61; 79)	77.3 (64.5; 80.4)	75.2 (66.1; 81.1)
Patients with stable angina (%)	62.0	58.5	57.9
Patients with previous MI (%)	30.2	29.3	30.4
Patients with hypertension (%)	86.8	70.7	74.4
Median of ejection fraction (%)	61.6 (50.6; 67.9)	65.4 (52.8; 69.4)	62.8 (51.5; 69.0)
Patients received cardiology treatment (%)			
ACE inhibitors/ACE receptors blockers	81.1	78.0	76.2
Aldosterone antagonists	75.5	70.7	73.2
β-blockers	81.1	82.9	80.6
Calcium antagonists	73.6	63.6	64.7
Antiplatelet agents	69.8	70.7	72.4
Diuretics	56.6	51.2	53.8

HF=Heart failure; GFR=Glomerular filtration rate; MI=Myocardial infarction; ACE=Angiotensin-converting enzyme

to the formula: total ID (mg) = body mass (kg) (normal Hb level [g/l] − patient's Hb level [g/l]) 0.24 + level of iron deposited (mg). Group II (n = 25) – patients who were treated with standard regimen without agreement on intravenous iron (III) hydroxide sucrose injections.

In the initial state, the patients of both the groups were comparable in terms of the main disease, indicators of age, duration of the disease, level of GFR, EF, FC of HF, systolic and diastolic blood pressure, and heart rate. The control comparison Group I consisted of 21 men with HFpEF and prostate cancer without ID anemia, comparable in age, cardiovascular risk profile, and obtained by treatment of HF. The comparison Group II consisted of 20 men with HFpEF and ID anemia without prostate cancer, comparable in age, cardiovascular risk profile, and obtained by treatment of HF.

All the patients were examined by physician, laboratory, and instrumental methods at the beginning and to the end of the study. The duration of observation in the hospital was 10 days, and then, the patients were observed in the outpatient department. The standard clinical and biochemical laboratory tests, blood tests for detection of ferritin, high sensitive C-reactive protein (hs-CRP), electrocardiogram examination were performed. Tolerability of the drug was determined on the basis of an assessment of laboratory parameters (the level of ALT, AST in the serum), the level of GFR, and the incidence of adverse reactions.

To evaluate the state of androgen deficiency, the testosterone level was determined by the method of immunoenzymatic analysis with the reagent test kit "AccuBind ELISA." Depending on the total testosterone level, the patients were divided into two groups: Group A (n = 32) – with androgen deficiency (total testosterone level below 2.5 ng/ml) – and Group B (n = 21) – without androgen deficiency (total testosterone levels >2.5 ng/ml).

Serum PAI-1 levels were determined using a modified colorimetric method of tPA determination (Rybachuk V., Savchuk O., Kharchenko S., Yatsenko T., Yusova O., Grinenko T. Assay for the determination of tPA activator. Patent UA113014. Issued 25.11.2016.). Exogenic recombinant tPA (Alteplase) was used as standard and PAI-1 activity (international units per mL, IU/mL) in serum samples was calculated by decrease of tPA activity: 1 IU tPA = 1 IU PAI-1.[24] Normal PAI-1 activity in blood plasma is 1–15 IU/mL. PAI-1 activity lower than 1 IU/mL indicates PAI-1 deficiency and is related to hyperfibrinolytic disorders, whereas activity higher than 15 IU IU/mL is associated with endothelial dysfunction and prothrombotic state.[25]

Serum CP levels were evaluated by immunoblot assay with the use of mouse monoclonal antibodies against human CP (E-9) (Santa Cruz Biotechnology, Inc., USA, cat. no. 365206). Briefly, patients' serum samples were mixed with Laemmli electrophoretic buffer, heated by 95°C for 5 min, and loaded onto 10% SDS-PAGE. After electrophoresis, proteins were transferred onto nitrocellulose membranes by electroblot. Then, membranes were blocked in 5% skim milk solved in phosphate-buffered saline containing 0.05%

Triton X-100 (PBST), at 37°C for 60 min. After blocking, membranes were incubated with the primary anti-CP antibodies diluted 1:1,000 at 4°C overnight. Unbound primary antibodies were washed out several times with PBST, and then, membranes were probed with the appropriate HRP-conjugated secondary anti-mouse IgG antibodies at 37°C for 90 min. After washing, immunoreactive bands were visualized by enhanced chemiluminescence (ECL) assay (Amersham, UK), digitized, and immunostaining intensities were analyzed with the use of TotalLab TL120 software (USA). Molecular weights were determined using standard prestained transblot molecular weight markers (PageRuler, Fermentas, Lithuania, cat. no. 26616). Quantified results of immunoblot assays were expressed as optical arbitrary units (a. u.).

The determination of FC HF was performed using a 6-min walk test. Quality of life was evaluated based on the Minnesota Living with HF Questionnaire (MLHFQ)[26] and quantitative Androgen Deficiency in Aging Males questionnaire (qADAM).[27] Clinical condition the patient was evaluated by the Scale score Clinical Status Assessment (SSCSA).[28] Determination of endothelial function was performed by flow mediated vasodilation of brachial artery at the baseline and after 4 weeks based on Celermajer's methodic.[23]

Statistical processing of the obtained results was performed using the licensed program STATISTICS. Nonparametric statistics were used. The data were presented in the form of a median (Me) and the interquartile segment (25%; 75%). For comparison of indicators in two independent groups, the Mann–Whitney U-test, the two-sided Fisher exact test, and the Wilcoxon test (W) were used to compare two dependent groups. Statistically significant differences in research results were determined at a level of $P < 0.001$.

RESULTS

At baseline, there were no statistically significant differences between the study groups' patients by the degree of anemia [$P > 0.001$, Table 1]. The median ferritin level in patients with HFpEF and prostate adenocarcinoma was 49.8 (32.5; 67.4) mg/ml which demonstrated ID status. There was an estimated significant correlation between ferritin level and level of EF – R = −0.78, $P < 0.001$.

The use of intravenous iron (III) hydroxide sucrose contributed to a significant increase in the level of Hb by 22.9% ($P < 0.001$), red blood cells count by 11.3% ($P < 0.001$), and ferritin by 150.5% ($P < 0.001$). In Group II, reliable changes in mentioned parameters were not detected ($P > 0.001$). The most significant differences were identified by ferritin level to the end of the observation [Table 2].

Dynamics of Hb was analyzed for the study period with the allocation intermediate point – 5 days [Figure 1]. Significant Hb Level change in the Group I began to appear from the 5th day (by 12.6%); however, the maximum level was observed by the 10th day.

Parenteral administration of trivalent iron caused normalization in Hb level in 53.6% of patients of Group I ($P < 0.001$), normalization in ferritin level in 82.1% ($P < 0.001$). By the end of the observation, a significant improvement in the clinical state was established with anemia correction with intravenous iron (III) hydroxide sucrose administration [Table 3]. Comparing treatment results in both the groups revealed a more intense dynamics of quality of life improving on scales SSCSA, MLHFQ, and qADAM with the use of intravenous iron (III) hydroxide sucrose. Average FC in the Group I decreased from 2.8 at the beginning to 2.3 to the end of observation ($P < 0.001$); in the same time, in Group II did not change significantly ($P > 0.001$).

Increased level of hs-CRP was established in 40 (75.5%) patients of main group and 14 (34.1%) of controls ($P < 0.001$). The median baseline hs-CRP level in patients with HFpEF and ID anemia with prostate cancer was 9.4 (5.8; 10.5) mmol/ml, in the 1st control group – 4.8 (4.0; 6.3) mmol/ml ($P < 0.001$), and in the 2nd control group – 5.7 (4.5; 6.8) mmol/ml ($P < 0.001$). The hs-CRP level correlated with ferritin level ($R = 0.75$, $P < 0.001$), Hb level ($R = 0.57$, $P < 0.001$), and serum iron level ($R = 0.68$, $P < 0.001$).

Analysis of the dynamics of the hs-CRP level revealed statistically significant differences in patients of the Group I and Group II after 10 days of treatment [Figure 2]. In the group of patients treated with intravenous iron (III) hydroxide sucrose, the median hs-CRP level decreased by 16.9% ($P < 0.001$), in Group II, this indicator was not significantly different.

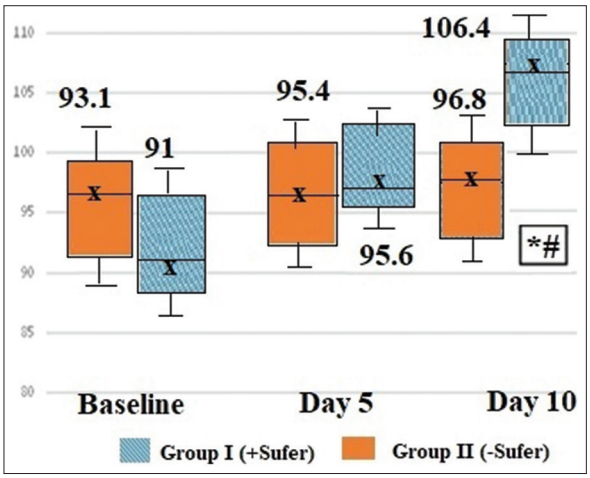

Figure 1: Dynamics of hemoglobin in patients of Group I and Group II during observation. *Significance of differences baseline and after observation, $P < 0.001$ (according to the Wilcoxon test); #Significance of differences in comparison with Group II, $P < 0.001$ (according to the Mann–Whitney test)

The majority of observed patients with HFpEF and ID anemia with prostate cancer had established baseline endothelial dysfunction - 42 (79.2%). The median baseline endothelium-dependent vasodilatation (EDVD) level was 4.4 (3.1; 5.5) % and was correlated with age ($R = -0.62$, $P < 0.001$), hs CRP level ($R = -0.54$, $P < 0.001$), and Hb level ($R = -0.63$, $P < 0.001$). The median baseline EDVD level in patients with HFpEF and ID anemia with prostate cancer was significantly lower in comparison with the 1st control group – 6.9 (5.6; 7.9) % ($P < 0.001$) and the 2nd control group – 7.8 (6.1; 8.4) % ($P < 0.001$). After 10 days of treatment with intravenous iron (III) hydroxide sucrose, it was estimated increased median EDVD by 14.5% ($P < 0.001$), in comparison with standard therapy - on 5.8% ($P > 0.001$). EDVD was significantly higher in Group I in comparison with the standard therapy group to the end of the study term ($P < 0.001$) [Figure 3].

The median baseline PAI-1 activity level in patients with HFpEF and ID anemia with prostate cancer was 75.74 (63.69; 87.79) U/mL, in the 1st control group – 58.78 (46.88; 69.52) U/mL ($P < 0.001$), and in the 2nd control group – 68.89 (58.49; 80.68) U/mL ($P < 0.05$). The PAI-1 activity level correlated with ferritin level ($R = 0.78$, $P < 0.001$), serum iron level (R = 0.48, $P < 0.001$), and testosterone level ($R = 0.67$, $P < 0.001$).

Analysis of the dynamics of the PAI-1 activity level revealed statistically significant differences in patients of Group I and Group II after 10 days of treatment [Figure 4]. In the group of patients treated with intravenous iron (III) hydroxide sucrose, the median PAI-1 activity level decreased by 9.2% ($P < 0.001$), in group II, this indicator was not significantly different.

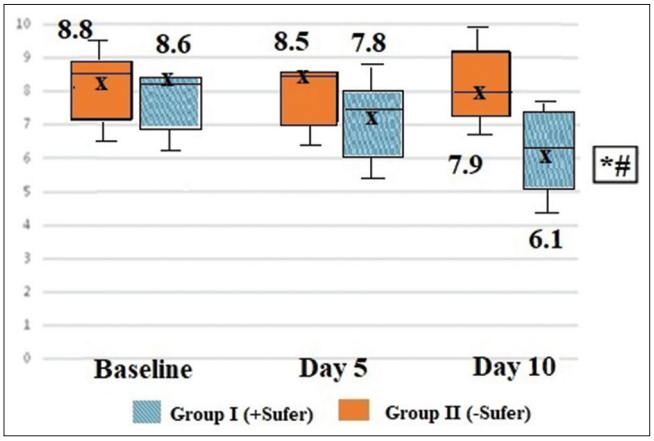

Figure 2: Dynamics of high-sensitive C-reactive protein level in patients of Group I and Group II during observation. *Significance of differences baseline and after observation, $P < 0.001$ (according to the Wilcoxon test); #Significance of differences in comparison with Group II, $P < 0.001$ (according to the Mann–Whitney test)

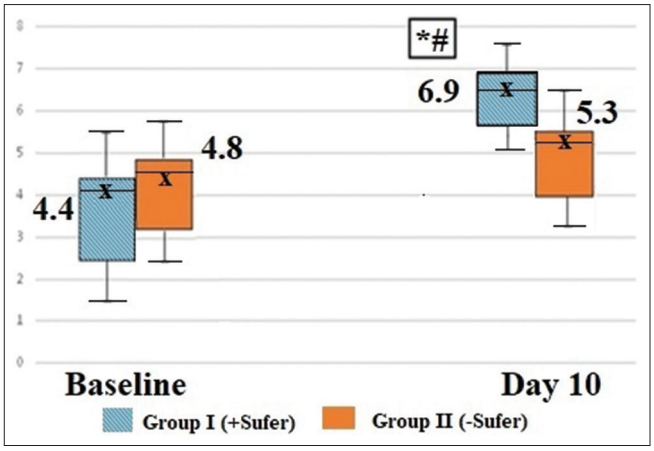

Figure 3: Dynamics of endothelium-dependent vasodilatation in patients of Group I and Group II during observation. *Significance of differences baseline and after observation, $P < 0.001$ (according to the Wilcoxon test); #Significance of differences in comparison with group II, $P < 0.001$ (according to the Mann–Whitney test)

Table 2: Dynamics of indicators of iron metabolism in men with iron-deficiency anemia and heart failure with preserved ejection fraction and prostate adenocarcinoma

Indicators	Group I		Group II	
	Baseline (n=28)	After 10 days of treatment with intravenous iron hydroxide sucrose (n=28)	Baseline (n=25)	After 10 days of standard treatment (n=25)
Erythrocytes, $\times 10^{12}$/l	3.7 (3.1; 4.0)	4.3 (3.7; 4.8)# Δ+0.6	3.5 (3.2; 4.0)	3.7 (3.5; 4.3) Δ+0.2
Hemoglobin, g/l	91 (89; 98.7)	106.4 (99.8; 111.7)# Δ+15.4	93.1 (88.7; 99.8)	96.8 (91.5; 100.5)* Δ+3.7
Ferritin, mg/ml	49.8 (32.5; 67.4)	168.9 (130.4; 176.6)# Δ+119.1	47.7 (32.8; 59.2)	59.2 (36.6; 66.1)* Δ+11.5
Serum iron, mcmol/l	5.7 (4.9; 6.7)	16.3 (11.5; 19.4)# Δ+10.6	5.8 (5.2; 6.4)	6.3 (5.5; 6.8)* Δ+0.5

*Significance of the differences between I and II Groups (P<0.001); #Significance of the differences between baseline indicators and after treatment (P<0.001)

The median baseline CP level was 4.58 (3.95; 5.21) arbitrary units (a. u.) and correlated with hs-CRP level (R = 0.48, P < 0.001), Hb level (R = −0.62, P < 0.001), serum iron level (R = −0.44, P < 0.001), and ferritin level (R = −0.70, P < 0.001). There were no statistically significant differences between CP level in patients of Group I and Group II at the onset of investigation. After 10 days of treatment with intravenous iron (III) hydroxide sucrose, it was estimated decreased median CP level by 35% (P < 0.001), in comparison with standard therapy – on 14.4% (P < 0.001) [Figure 5].

There were no significant side effects with the inclusion of intravenous iron (III) hydroxide sucrose to the standard therapy in the dynamics of observation, and there was no need to change the daily dose or discontinue treatment. At the end of the observation, the levels of ALT, AST, and bilirubin did not change significantly in comparison with the initial state. Thus, the results of the study indicate the effectiveness of intravenous iron (III) hydroxide sucrose in complex treatment of patients with ID anemia and HFpEF and prostate cancer, which reflects an improvement in HF FC, quality of life, endothelial function, hs-CRP, PAI-1, and CP level decreasing in parallel with an increase in Hb and normalizing ferritin levels.

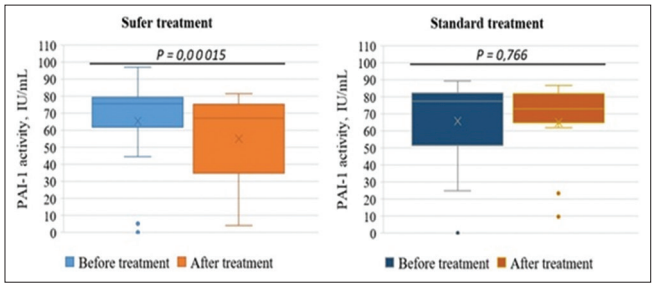

Figure 4: Intravenous iron (III) hydroxide sucrose treatment attenuates plasminogen activator inhibitor-1activity in patients with iron-deficiency anemia and heart failure with concomitant prostate cancer, paired Wilcoxon *t*-test

DISCUSSION

As known, the pathogenesis of ID in oncological patients is complex and depends on multiple factors. The prevalence of ID in patients with different cancer ranges from 32% to 60%.[29] The recent year's trials have demonstrated superior efficacy of intravenous iron over oral in reducing blood transfusions, increasing Hb, and improving quality of life in erythropoiesis-stimulating agent treated cancer patients, and no serious drug-related adverse effects were seen.[30] Thus, the European Society For Medical Oncology Clinical Practice Guidelines suggest that initiation of anemia treatment with intravenous iron alone should be investigated as a treatment option for cancer-related anemia.[31]

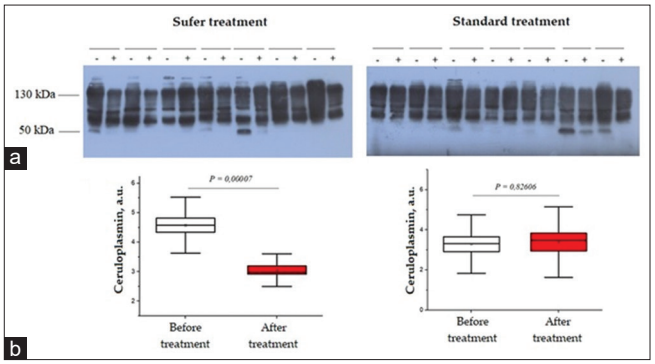

Figure 5: Intravenous iron (III) hydroxide sucrose treatment decreases ceruloplasmin levels in patients with iron-deficiency anemia and heart failure with concomitant prostate cancer: (a) representative immunoblots of ceruloplasmin polypeptides, (b) densitometry analysis of immunoblots, paired *t*-test. a. u. = Arbitrary units, − = Before treatment, + = After treatment

Table 3: Dynamics of clinical assessment of patients with iron-deficiency anemia and heart failure with preserved ejection fraction and prostate adenocarcinoma

Indicators	Group I		Group II	
	Baseline (n=28)	After 10 days of treatment with intravenous iron hydroxide sucrose (n=28)	Baseline (n=25)	After 10 days of standard treatment (n=25)
SSCSA	3.9 (3.1; 4.1)	3.0 (2.6; 3.6)[#] Δ−0.9	3.7 (3.2; 4.0)	3.5 (3.1; 3.8) Δ−0.2
Test with 6 min walking	259.4 (231.8; 271.7)	310.7 (278.8; 325.4)[#] Δ+51.3	262.6 (238.2; 269.8)	275.9 (247.5; 281.7)* Δ+13.3
MLHFQ	54.1 (42.5; 67.4)	40.9 (37.5; 46.6)[#] Δ−13.2	52.7 (47.8; 65.7)	48.1 (42.2; 58.8)* Δ−4.6
qADAM	28.7 (20.7; 34.6)	41.3 (34.5; 49.6)[#] Δ+12.6	25.9 (20.2; 33.1)	32.4 (24.4; 37.8)* Δ+6.5

*Significance of the differences between I and II Groups (P<0.001); [#]Significance of the differences between baseline indicators and after treatment (P<0.001). SSCSA=Scale Score Clinical Status Assessment; MLHFQ=Minnesota Living with Heart Failure Questionnaire; qADAM=quantitative Androgen Deficiency in Aging Males questionnaire

Two large analyses demonstrated the relationship between Hb levels and physical activity and quality of life in cancer patients.[32] Hb increase achieved with intravenous iron supplementation of erythropoiesis-stimulating agents treatment in patients with chemotherapy-related ID anemia was associated with significantly better effects on physical activity and overall quality of life ($P < 0.0002$).[33]

Anemia has recently been recognized as an important comorbid condition and potentially novel therapeutic target in patients with HF. Anemia is common in HF patients, with a prevalence ranging from 4% to 55% depending on the population studied. Multiple potential mechanisms of interaction exist between anemia and the clinical syndrome of HF, including hemodilution, inflammatory activation, renal insufficiency, and malnutrition.

A large meta-analysis of trials, who received IV iron therapy, examining the effects of IV iron therapy in ID patients with systolic HF, demonstrated a significant reduction in the risk of all-cause death or cardiovascular hospitalization, resulted in a significant reduction in NYHA class, an increase in the 6-min walking test distance, and an improvement in quality of life.[34] The present research showed intravenous iron (III) hydroxide sucrose supplementation in complex treatment of patients with ID anemia and HFpEF with concomitant prostate cancer has contributed to significant improvement of life quality based on both specific scales for HF patient (MLHFQ) and Androgen Deficiency scale (qADAM) ($P < 0.001$).

There are numerous data showed a central role in the pathogenesis of anemia in HF to inflammatory mediators. Zhou *et al*. meta-analysis suggests that intravenous iron therapy can reduce HF hospitalization, improve quality of life, and decrease serum levels of NT-proBNP and CRP in patients with HF.[35] The present data have demonstrated that administration of intravenous iron (III) hydroxide sucrose in complex treatment of patients with ID anemia and HFpEF with concomitant prostate cancer induced significant decrease in CRP level and endothelial dysfunction improving ($P < 0.001$) that could be beneficial for this category of patients.

Recent literature from observational databases and clinical trials suggests that anemia is an independent risk factor for adverse outcomes in patients with HF, it is not generally regarded as a factor affecting the blood's coagulability (Lawler *et al*.,). ID anemia seems to be a novel risk factor for thrombosis, while the mechanism for this is not fully understood, especially in case of HF. The present study has demonstrated that patients with HFpEF and ID anemia with concomitant prostate cancer are characterized by the increased level of coagulability associated with ID degree and testosterone level. Intravenous iron (III) hydroxide sucrose in complex treatment of patients with ID anemia and HFpEF with concomitant prostate cancer induced significant decrease of coagulability level ($P < 0.001$). The decrease in PAI-1 activity and circulating CP level can be explained by the indirect influence of the CRP normalizing and by ID correction. However, a direct effect of treatment with intravenous iron (III) hydroxide sucrose on coagulability reduction is also possible that requires further research.

Search for therapeutic options of ID correction to improve prognosis in patients with HFpEF remains a relevant problem. Long-term follow-up studies are also necessary to evaluate the safety of III iron intravenous therapy and hard endpoints for outcomes in this population of complex comorbid patients.

Limitations

However, this study should be interpreted with several limitations. Therefore, only patients with HFpEF with prostate cancer were chosen for this study, and consequently, the results can only be applied to this population. It could be perspectival to evaluate the hard endpoint with prolongation of this therapy.

CONCLUSION

The present study has demonstrated that patients with HFpEF and ID anemia with concomitant prostate cancer are characterized by endothelial dysfunction and increased activity of PAI-1 and circulating CP level. The infusion of intravenous iron (III) hydroxide sucrose in these patients contributed to anemia correction with significant improvement in clinical condition, quality of life, tolerance to physical activity, and addition decreasing of coagulability and hs-CRP level.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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