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The experience of using ACE inhibitors and Ca channel blockers in the treatment of hypertension in patients with renal cell carcinoma

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Abstract

Renal cell carcinoma (RCC) is one of widely spread urological cancers. It is known that approximately 26% of patients with a history of kidney cancer (KC) may have concomitant coronary artery disease, hypertension, diabetes mellitus and some other systemic diseases, which may lead to nephrosclerotic changes and the development or progression of the existing CRF.

The aim of the study. To study the renal function effects of ACE inhibitors (perindopril arginine) in patients with RCC, both as monotherapy and in combination with Ca channel blockers when conducting treatment of concomitant hypertension (HT).

Materials and methods. The study enrolled 38 patients with RCC. All patients were diagnosed with RCC for the first time, with their cancer staged according to the TNM International Classification (T_1 N_0 M_0).

Within a month, the use of combination therapy for kidney cancer complicated by Stage I, Degree II hypertension was leading to increases in serum creatinine by 3 μmol/l and by 7 μmol/l in those patients where combination therapy was not used. In the meantime,

during the same period, glomerular filtration rate reduced by 5 ml/min/1.73 m^2 in patients of the first group and by 15 ml/min/1.73 m^2 in patients of the second group.

Key words: renal cell carcinoma; hypertension; kidney cancer

Hypertension (HT) is one of the most important medical and social problems of today. Along with hypertension, patients usually have a number of other comorbidities. Among them, a group of diseases of the highest medico-demographic importance can be distinguished, namely: urolithiasis, chronic renal failure (CRF), prostatic disease, chronic pyelonephritis and kidney cancer. Renal cell carcinoma (RCC) is one of widely spread urological cancers. It is known that approximately 26% of patients with a history of kidney cancer (KC) may have concomitant coronary artery disease, hypertension, diabetes mellitus and some other systemic diseases, which may lead to nephrosclerotic changes and the development or progression of the existing CRF.

According to modern literature data, the prevalence of CRF in Ukraine is approximately 7-10%; more than 500 thousand patients have signs of CRF, the progression of which is ultimately leading to complete loss of kidney function [1, 2]. Conducting surgical treatment of patients with RCC, especially with an intraoperative use of organ ischemia, may subsequently deteriorate the functional state of the kidneys. The main reasons for the disappointing statistics include the development or further progression of chronic kidney disease (CKD).

The reasons for the lack of efficacy of pharmacological approaches include the following: predominant use of drugs that have been marketed for many years, formation of interrelated renal/multi-organ dysfunction (syndromes), nephrotoxicity of background therapies for comorbid or polymorbid conditions associated with nephropathy, as well as the challenges of implementing the results of experimental nephrology in health care practice.

Thus, implementation of the objective of nephroprotection in patients with RCC concerning slowing down the progression of kidney disease, improving the quality of life and especially the survival in this patient population, calls for a multifaceted approach, where drug products are playing a key role.

A very large number of randomized trials have investigated the effect of antihypertensive drugs on various renal endpoints, e.g. microalbuminuria or proteinuria, glomerular filtration rate (GFR) and the incidence of terminal stages of kidney disease in various medical conditions, such as diabetes, diabetic nephropathy, non-diabetic kidney disease or "conventional" hypertension. Given the heterogeneity of the clinical conditions

where these endpoints are used, this problem is not ideal for meta-analyzes. Probably the best approach here will be a critical and selective review of the available data [3, 4, 5].

The nephroprotective effects of antihypertensive agents, chiefly ACE inhibitors and angiotensin receptor antagonists, have been studied in multiple randomized trials. A number of placebo-controlled studies have shown that these drug classes or a low-dose ACE inhibitor combined with a diuretic slow down the development of end-stage renal disease or a significant increase in serum creatinine, and improve or prevent microalbuminuria or proteinuria in patients with both diabetic and non-diabetic nephropathy. Anti-proteinuric effects in contrast to placebo have also been shown with the use of spironolactone. With the exception of one trial, in all other placebo-controlled studies, the renal effects of the active ingredient were accompanied by a somewhat greater reduction of blood pressure, which was at least partially responsible for renal effects. In fact, the SYST-EUR study found that a calcium antagonist (nitrendipine) preserved renal function better than placebo. [7, 8].

Comparison of various active treatment regimens provided less clear results. Two studies, one in patients with proteinuric diabetic nephropathy, and the other in patients with non-diabetic nephropathy, showed higher efficacy of angiotensin receptor antagonists or angiotensin-converting enzyme (ACE) inhibitors compared to calcium channel blockers in delaying end-stage renal disease and in delaying a significant increase in serum creatinine. However, a sub-analysis within the ALLHAT study in hypertensive patients with reduced renal function has initially shown (no data of proteinuria was present) a similar incidence of these endpoints in patients treated with a diuretic, calcium antagonist or an ACE inhibitor. The studies where GFR was assessed, have also yielded ambiguous results: only one of these studies has shown a somewhat lesser reduction in this parameter when an ACE inhibitor was used vs. a beta-adrenergic blocker or a calcium antagonist, while other studies have not demonstrated any dissimilar effects of ACE inhibitors compared to a calcium antagonist, a beta-adrenergic blocker, an angiotensin receptor antagonist or a combination of a calcium channel blocker with a diuretic; similar effects of calcium antagonists and diuretics have also been demonstrated in one of the studies [9, 10].

Less clear results have been obtained concerning the comparative impact of different antihypertensive drugs on microalbuminuria or proteinuria. Angiotensin receptor blockers have appeared more effective in reducing excretion of protein in the urine compared with beta-adrenergic blockers, calcium antagonists or thiazide diuretics; aldosterone antagonists were superior to calcium antagonists, and ACE inhibitors were superior to calcium channel blockers. It should be kept in mind that the results were quite heterogeneous; however,

according to reports, ACE inhibitors were non-inferior to calcium antagonists in three studies, and non-inferior to diuretics in one study.

Several recent studies are interesting, which evaluated a combination of an angiotensin receptor antagonist with an ACE inhibitor (compared to monotherapy). The COOPERATE study reported delayed progression of non-diabetic nephropathy with the use of a combination of drugs vs. monotherapy with individual components, with no differences in blood pressure readings between major groups. Other studies have shown a greater antiproteinuric effect of combination therapy, which was associated with a more pronounced reduction in blood pressure (BP). Indeed, when the dose of an ACE inhibitor was titrated to the level to obtain a BP reduction typical for the combination regimen, no difference in the antiproteinuric effect was detected. The available studies were included into the most recent meta-analysis, which has confirmed a better antiproteinuric effect of combined therapy associated with a greater decrease in BP. On the other hand, two small studies allow suggesting that very high doses of angiotensin receptor antagonists may implement a much greater antiproteinuric effect compared to standard doses, without an increase in the hypotensive effect. Such conclusions require confirmation on larger patient populations [11, 12].

Thus, to date there is no clear data on the renal function effects of ACE inhibitors (perindopril arginine) in patients with RCC, both as monotherapy and in combination with Ca channel blockers when conducting treatment of concomitant hypertension (HT).

The aim of the study. To study the renal function effects of ACE inhibitors (perindopril arginine) in patients with RCC, both as monotherapy and in combination with Ca channel blockers when conducting treatment of concomitant hypertension (HT).

Materials and methods

The study enrolled 38 patients with RCC. All patients were diagnosed with RCC for the first time, with their cancer staged according to the TNM International Classification (T_1 N_0 M_0). Fuhrman histological grading: G_1 – G_3, histological subtype of RCC: clear cell carcinoma. All patients had a therapeutic kidney resection. In addition to that, Stage I, Degree II HT was observed in both test groups (moderate HT), i.e. systolic blood pressure (sBP) at 160 to 179 mm Hg, diastolic blood pressure (dBP) at 100 to 109 mm Hg. In the meantime, there were no statistically significant differences between the two groups in terms of mean systolic and diastolic pressures ($p>0.05$).

The first group enrolled 17 patients. In addition to the aforementioned surgical treatment, all patients of Group I were given Bi-PRESTARIUM®, a therapeutic combination of an ACE inhibitor (perindopril arginine 5 mg) and a Ca channel blocker (amlodipine 5 mg)

for the treatment of HT. The second group enrolled 21 patients, who, unlike the patients in Group I, used only ACE inhibitors (perindopril arginine 5 mg) to treat their HT. The main treatment efficacy criteria included the following: 1) serum creatinine level; 2) GFR. Evaluation of the results was conducted at the initial visit of the patient to the healthcare institution, and in 1 and 3 months following the initial visit. Statistical data were processed using applied statistical methods with Microsoft Excel 2016 software package.

Results and discussion

As a result of the treatment, there was a statistically significant reduction in mean values of systolic and diastolic pressure to normal values in both study groups during 3 months of follow-up, as shown in Table 1.

During 3 months of follow-up, patients of study Group II had a statistically significant increase in mean values of serum creatinine level and an increase in GFR compared to patients of Group I.

Table 1. Changes in renal function with time before treatment and in 1 and 3 months from the onset of treatment

Observation period	Assessment criterion					
	Serum creatinine level, μmol/l			GFR ml/min/1.73 m^2		
	At primary examination	In 1 month	In 3 months	At primary examination	In 1 month	In 3 months
Group I (n=17)	109 ± 0.15	112 ± 2.13	114 ± 2.72	89 ± 4.24	84 ± 7.61	81 ± 6.22
Group II (n=21)	107 ± 0.13	114 ± 1.28	121 ± 3.72	89 ± 1.73	74 ± 1.11	58 ±3.17

On average, in 1 month of observation, the use of a combination therapy for kidney cancer complicated by Stage I, Degree II HT has led to an increase in serum creatinine by 3 μmol/l in patients of the first group and by 7 μmol/l in patients of Group II. Accordingly, the average reduction in GFR in the aforementioned groups of patients was 5 ml/min/1.73 m^2 in patients of the first group and 15 ml/min/1.73 m^2 in patients of the second group during the same period.

On average, in 3 months from the onset of treatment, in a setting of combination therapy for kidney cancer complicated by Stage I, Degree II HT, there was an increase in serum creatinine by 5 μmol/l in patients of the first group and by 14 μmol/l in patients of Group II. Accordingly, in 3 months from the onset of treatment, the average reductions in

GFR were 8 ml/min/1.73 m^2 in patients of the first group and 31 ml/min/1.73 m^2 in patients of the second group.

Conclusions

Within a month, the use of combination therapy for kidney cancer complicated by Stage I, Degree II hypertension was leading to increases in serum creatinine by 3 μmol/l and by 7 μmol/l in those patients where combination therapy was not used. In the meantime, during the same period, glomerular filtration rate reduced by 5 ml/min/1.73 m^2 in patients of the first group and by 15 ml/min/1.73 m^2 in patients of the second group.

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