Archives of Gerontology and Geriatrics 53 (2011) 60–63

Contents lists available at ScienceDirect

Archives of Gerontology and Geriatrics

journal homepage: www.elsevier.com/locate/archger

Losartan vs. amlodipine treatment in elderly oncologic hypertensive patients: A randomized clinical trial

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ARTICLE INFO

Article history:
Received 4 January 2010
Received in revised form 20 April 2010
Accepted 22 April 2010
Available online 31 May 2010

Keywords:
Losartan
Amlodipine
Uric acid
Hypertension
Renal function of elderly

ABSTRACT

Elderly neoplastic patients frequently may show hypertension and hyperuricemia, before and after chemotherapeutic treatments. The purpose of this study was to evaluate the efficacy of losartan which is an antihypertensive drug with uricosuric properties vs. amlodipine in hypertensive neoplastic elderly patients. This was an open-labeled, randomized, comparative trial. The study was performed as a 30-day study. Seventy patients with cancer were randomly assigned to receive losartan or amlodipine. Blood pressure (BP), blood urea nitrogen (BUN) levels, creatinine, serum and urinary uric acid, creatinine and uric acid clearance were determined before and after chemotherapy. One day after chemotherapy in losartan group vs. amlodipine group we observed a significant difference in urinary uric acid ($p < 0.001$) of 18 mg/24 h vs. 40 mg/24 h. Thirty days after chemotherapy we observed a significant difference in azotemia of 0.0 mg/dl vs. 3.8 mg/dl ($p < 0.001$), serum uric acid of 0.05 mg/dl vs. 0.49 mg/dl ($p < 0.001$), urinary uric acid ($p < 0.001$) of 23 mg/24 h vs. 0.0 mg/24 h, GFR of 2 ml/min/1.73 m^2 vs. −8 ml/min/1.73 m^2 ($p < 0.05$) and systolic BP (SBP) of 3.6 mmHg vs. 0.8 mmHg ($p < 0.05$). The findings of the present study support the effective role of losartan compared to amlodipine in treating hypertension and hyperuricemia in elderly patients under chemotherapeutic treatment.

1. Introduction

Cancer and hypertension are important worldwide public-health challenges because of their high frequency and concomitant risks and co-morbidities (Repetto et al., 1998; Di Mauro et al., 2000, 2002). For most types of cancer, incidence rates increase with advancing age. Over 50% of all new cancer cases are diagnosed in people aged 65 years or older, and over 60% of all cancer deaths occur in this group of population. Hypertension has been identified as the leading risk factor for mortality, and is ranked third as a cause of disability-adjusted life-years. It is among the most frequent chronic co-morbidities associated with cancer together with arthrosis, cerebral vasculopathies, diabetes mellitus, cardiopathies, chronic obstructive pulmonary disease (COPD) and many others (Malaguarnera et al., 2000). Moreover oncologic patients are affected by problems deriving by the standard treatment used in malignancies such as aggressive cytotoxic agents, radiotherapy or immune-therapy (Malaguarnera et al., 2001, 2010). Several side effects might derive from these treatments, particularly hyperuricemia developed from tumor lysis syndrome (TLS) (Rampello et al., 2006; Cammalleri and Malaguarnera, 2007; Pumo et al., 2007). Nevertheless uric acid is also commonly associated with hypertension. Uric acid is present in 25% of untreated hypertensive subjects, in 50% of subjects taking diuretics, and in >75% of subjects with malignant hypertension (Baker et al., 2005). Specially uric acid levels correlate with prehypertension, hypertension, increased proximal sodium reabsorption, microalbuminuria, proteinuria, kidney disease, obesity, hypertriglyceridemia, low high-density lipoprotein chole-sterol, hyperinsulinemia, hyperleptinemia, hypoadiponectinemia, peripheral, carotid and coronary artery disease, endothelial dysfunction, oxidative stress, renin levels, endothelin levels, and C-reactive protein levels (Malaguarnera et al., 2009). Losartan is the prototype of highly selective angiotensin 1 (AT_1) receptor-antagonist. It has been approved for the treatment of hypertension alone or in combination with other antihypertensive agents (Billet et al., 2008). The

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doi:10.1016/j.archger.2010.04.022

aim of the present study was designed to establish if losartan is effective in treating hypertension and preventing the typical elevation in serum uric acid levels caused by chemotherapy.

The study protocol was approved by the research ethics committee of Cannizzaro Hospital, Catania, Italy, and was performed in accordance with the Declaration of Helsinki principles and the Good Clinical Practice Guidelines (WMAD, Helsinki, 2004).

2. Subjects and methods

2.1. Patients

Between January 2001 and November 2005, a total of 70 elderly patients (29 males and 41 females) that came under attention in our department were enrolled. Eligibility criteria included patients with a history of hypertension (SPB and/or diastolic BP = DBP) and cancer. The cohort was equally divided into two different groups according to drug used to treat hypertension: 35 patients received losartan (Group L) and 35 received amlodipine (Group A). The mean patient's age of Group A was 74 ± 4.6 and of Group L was 76 ± 3.8. The mean SBP and DBP were, respectively, 142.1 ± 8.9 mmHg and 81 ± 11 mmHg in Group L; while, in Group A the same values were 148.7 ± 7.1 mmHg, and 82 ± 9, respectively. There was quite a wide spectrum of tumors: 7 patients had hepatocarcinoma, 13 had microcytoma, 21 had breast cancer, 23 had colorectal carcinoma and 6 had pancreatic carcinoma. Informed consent has been obtained from all participants, after the type and phases of study were been fully explained. Patients were excluded from the study if they had a history of clinically significant atopic allergy (allergic rush or anaphylaxia), bronchial asthma, excessive alcohol intake.

2.2. Methods

Blood samples were obtained after the patients had fasted for 12 h overnight. Venous blood samples were taken from all patients between 8 a.m. and 10 a.m. We used plasma obtained from the blood samples by the addition of EDTA and centrifugation at $3000 \times g$ for 15 min at 4 °C (Vacutainer SST II Advance, BD Plymouth, UK). Immediately after centrifugation, the plasma samples were frozen and stored at −80 °C. Uric acid was assayed with the uricase method with intra and interassay coefficients of variability (CVs) of 0.7% and 2.8%, respectively (Hitachi 704 analyzer reactive). Serum creatinine level was measured using a modified Jaffè reaction with intra and interassay CVs of 0.6% and 2.7%, respectively (Blass et al., 1974).

GFR (glomerular filtration rate) was estimated from the following equation: GFR: $186 \times (\text{serum creatinine}) - 1.154 \times (\text{age}) - 0.203 \times (0.742 \text{ if female})$. We used a slightly modified version of Charlson co-morbidity index for recording co-morbidity (Charlson et al., 1987).

2.3. Efficacy and tolerability assessment

During treatment, patients were advised to continue diet and physical activity if they had already been doing so (although they were not instructed to begin these lifestyle changes for the purpose of the study). We told our patients to continue their standard diet not modifying their salt intake during the period of the study, because it may represent a confounding factor. Patients already treated, before the study, with antihypertensive drugs were invited to interrupt the treatment for a wash-up period of 7 days (Phase 1).

Our study was carried out in 4 phases, evaluating the effects of the administered drugs before and after chemotherapy. We determined BP pressure, azotemia, creatininemia, serum and urinary uric acid before chemotherapy (Phase 2), 1 day after treatment (Phase 3) and 30 days after treatment (Phase 4). All patients began treatment with a once-daily, single dose of losartan (50 mg/day) to Group L and amlodipine (10 mg/day) to Group A for 30 days. Patients were randomized to either losartan or amlodipine. At each visit, the patients underwent a complete physical examination and blood samples were taken to measure azotemia, creatininemia, uricemia. The protocol included the survey of plasmatic and urinary levels of urate and its clearance performed on 24 h urine samples. SBP and DBP were measured to the nearest 2 mmHg with a standard sphygmomanometer on the right arm of subjects sitting after 5 min rest. Patients were also asked about their clinical symptoms including any drug adverse effects. SBP and DBP, azotemia, creatininemia, serum and urinary uric acid were measured. The protocol was approved by the institutional review board.

2.4. Statistical analysis

We compared the data of the two groups and *t*-test statistical analysis was performed to evaluate the changes in laboratory values. The level of significance was set at $p < 0.05$. The difference between the two groups was calculated considering the difference between data of the Group L and A. Efficacy was assessed as significant statistical changes in laboratory data during the different phases of the study in the two groups.

3. Results

Baseline clinical and demographic characteristics were similar between the two treatment groups. There was no significant difference in smoking between the groups (Tables 1 and 2).

3.1. Effects of losartan

In patients treated with losartan we observed a significant increase of azotemia ($p < 0.001$; 95% confidence (CI) interval = 19.31–15.29), creatininemia ($p < 0.001$; CI = −0.50 to −0.14), serum uric acid ($p < 0.001$; CI = 3.25–2.56) and SBP ($p < 0.05$; CI = −11.09 to −1.31) 1 day after chemotherapy.

Table 1
Baseline features of the patients, *n*, mean ± SD.

General characteristics	Losartan group	Amlodipine group
Number	35	35
Age, years	74.0 ± 4.6	76.2 ± 3.8
Sex (male/female)	14/21	15/20
SBP (mmHg)	142.1 ± 8.9	148.7 ± 7.1
DBP (mmHg)	81 ± 11	82 ± 9
Heart rate (beats/min)	84 ± 6	86 ± 7
Hepatocellular carcinoma	3	4
Microcytoma	7	6
Breast cancer	11	10
Colorectal cancer	10	13
Pancreatic cancer	4	2

Notes: There were no significant differences between the groups.

Table 2
Laboratory findings of the patients at enrolment (Phase 1).

General characteristics	Losartan group	Amlodipine group
Azotemia (mg/dl)	50.2 ± 4.4	48.6 ± 6.1
Creatininemia (mg/dl)	1.00 ± 0.20	0.98 ± 0.25
Serum uric acid (mg/dl)	6.90 ± 1.84	6.44 ± 1.82
Urinary uric acid (mg/24 h)	625 ± 144	638 ± 122
GFR rate (ml/min/1.73 m2)	96 ± 13	97 ± 12

Notes: There were no significant differences between groups.

Table 3
The results of the sturdy on the examined parameters, mean ± SD.

	Losartan group			Amlodipine group		
	Before	1-Day after	30-Day after	Before	1-Day after	30-Day after
Azotemia (mg/dl)	46.8 ± 5.3^{B}	$64.1 \pm 2.7^{***,C}$	$46.8 \pm 4.4^{*,A}$	50.2 ± 5.7^{B}	$63.2 \pm 3.8^{***,C}$	$54.0 \pm 4.9^{**,A}$
Creatininemia (mg/dl)	0.96 ± 0.37^{C}	$1.28 \pm 0.38^{***,C}$	$0.94 \pm 0.36^{*,C}$	1.04 ± 0.32^{C}	$1.24 \pm 0.36^{**,C}$	$1.08 \pm 0.44^{*,C}$
Serum uric acid (mg/dl)	5.05 ± 0.85^{A}	$7.96 \pm 0.58^{***,C}$	$5.10 \pm 1.2^{*,A}$	6.31 ± 1.42^{A}	$7.84 \pm 0.62^{***,C}$	$7.18 \pm 1.3^{**,A}$
Urinary uric acid (mg/24 h)	776 ± 184^{A}	$826 \pm 134^{*,A}$	$799 \pm 126^{*,A}$	644 ± 132^{A}	$662 \pm 161^{*,A}$	$644 \pm 118^{*,A}$
GFR (ml/min/1.73 m^2)	94 ± 12^{C}	$99 \pm 10^{*,C}$	$96 \pm 14^{*,B}$	95 ± 13^{C}	$94 \pm 12^{*,C}$	$87 \pm 13^{**,B}$
SBP (mmHg)	148.8 ± 9.2^{C}	$155.6 \pm 11.2^{**,C}$	$145.2 \pm 8.4^{*,B}$	149.8 ± 10.2^{C}	$158.1 \pm 10.2^{***,C}$	$149.0 \pm 6.1^{*,B}$
DBP (mmHg)	84.7 ± 7.8^{C}	$88.2 \pm 8.1^{*,C}$	$85.4 \pm 6.9^{*,C}$	86.7 ± 4.7^{C}	$86.8 \pm 4.9^{*,C}$	$88.1 \pm 5.4^{*,C}$

Notes: Comparison within groups according to the values before chemotherapy: $^{*}p$ = not significant; $^{**}p < 0.05$; $^{***}p < 0.001$. Comparison between groups at the same phases of treatment: $^{A}p < 0.001$; $^{B}p < 0.05$; ^{C}not significant.

3.2. Effects of amlodipine

In patients treated with amlodipine there was a significant increase in the following parameters one day after chemotherapy: azotemia ($p < 0.001$; CI = −15.31 to −10.69), creatininemia ($p < 0.05$; CI = −2.05 to −1.01), serum uric acid ($p < 0.001$; CI = −2.05 to −1.01), SBP ($p < 0.001$; CI = −13.17 to −3.43). 30 days after chemotherapy we observed a significant increase in azotemia ($p < 0.05$, CI = −6.34 to −1.26), serum uric acid ($p < 0.05$, CI = −1.52 to −0.22) and GFR ($p < 0.05$, CI = 2.56–15.44).

3.3. Comparison between treatments

One day after chemotherapy in Group L vs. Group A, we observed a significant difference in urinary uric acid ($p < 0.001$) 18 mg/24 h vs. 40 mg/24 h, and 30 days after chemotherapy we observed a significant difference in azotemia 0.0 mg/dl vs. 3.8 mg/dl ($p < 0.001$), serum uric acid 0.05 mg/dl vs. 0.49 mg/dl ($p < 0.001$), urinary uric acid ($p < 0.001$) 23 mg/24 h vs. 0.0 mg/24 h, GFR 2 ml/min/1.73 m^2 vs. −8 ml/min/1.73 m^2 ($p < 0.05$) and SBP-change 3.6 mmHg vs. 0.8 mmHg ($p < 0.05$) (Table 3).

3.4. Adverse events

No serious adverse events were reported in either of the groups.

4. Discussion

Our study demonstrated that losartan confers renal protection by reducing azotemia and creatininemia levels in serum, moreover it improved GFR reducing the risk of renal failure. The damages derived from hyperuricemia per se and the complications linked to high acid uric levels were reduced. The primary benefit appeared to be the effect on the renal component increasing uric acid excretion too. Given that there is no uric acid peak in blood limiting the risk of acute gout arthritis attacks, formation of calculi and acute renal failure (ARF). We cannot exclude that losartan had beneficial effect on the renal outcomes because it had antihypertensive and hypouricemic effects. It can be expected that the potent uricosuric action of losartan might be a cause of increased incidence of urinary calculosis, because of the possible urine supersaturation (Hamada et al., 2002). The biggest concern using losartan involves the risk of incidence of urinary calculosis. We had none, probably because of a urine alkalinization effect that hampers the formation of crystals (Shahinfar et al., 1999). The uricosuric action of losartan is not linked to renin–angiotensin system. The site of action is the urate/anion exchanger, called URAT 1, located on the surface of the epithelial cells of proximal tubule. This transporter that reabsorbs urate has been recently identified by Enomoto et al. (2002). The same uricosuric effect was also demonstrated in eprosartan, another AT-II-blocker, but losartan resulted twenty fold more effective than its metabolite E-3174 and eprosartan itself in blocking the exchanger with a mechanism both dose dependent and competitive. Moreover losartan is six–seven-fold more effective also than probenecid in inhibiting urate uptake. URAT-1 is also a site of action for antiuricosuric drugs such as diuretics that increase uricemia causing a extracellular volume reduction.

Two mechanisms may explain these properties: either a bond or a competition with URAT-1 (Roch-Ramel et al., 1997). The significant uricosuric effect is obtained with the normal dosages used in antihypertensive therapy and, also, in the chronic therapy. Other authors underlined that this effect persist for a period no longer than two months, probably because a new steady-state in uric acid metabolism is reached or an up-regulation of URAT-1 occurred. Several studies were performed so far in order to assess the antihypertensive and uricosuric activities of some drugs but just losartan resulted the only one, among those tested, having a clinically relevant uricosuric activity (Rayner et al., 2006). Other studies reported a transient uricosuric effect of calcium-antagonists and ACE-inhibitors but uric acid excretion raises to 10–30% in respect of the 300% observed using losartan.

The probenecid-like action of losartan is dose dependent and begins within 4 h after administration. It is noteworthy that the dosage of losartan 50 mg twice a day does not increase the uricosuric effect in respect of the normal dosage of 50 mg once a day. Indeed, the effect of losartan becomes evident independently from the diet intake of sodium (Elliott et al., 2001). Several studies have also demonstrated that losartan might protect kidney, myocardium, liver and brain from the age-dependent histological changes (Osawa et al., 2006). In hypertensive patients, not suffering from diabetes, and with proteinuria, losartan significantly reduces proteinuria and albumin and IgG urinary fraction of excretion (Lozano et al., 2001). In the multicentric, double-blinded RENAAL (Reduction of Endpoints in NIDDM with the Angiotensin II receptors Antagonist Losartan) study, losartan in the context of a conventional therapy (that may include diuretics, calcium-antagonists, α- or β-blockers and other antihypertensive drugs with central action with exclusion of ACE-inhibitors and AT-II-antagonists) determined protective effects on kidneys in hypertensive patients with type II diabetes and nephropathy.

The results of this study showed that the treatment with losartan associated with a conventional therapy can determine a significant reduction in the risk indicated by the primary composed endpoint represented by the doubling of serum creatinine levels, terminal renal failure (need of dialysis o transplant) or death compared to placebo plus conventional therapy (Kurokawa et al., 2006). The above mentioned nephroprotective effect of losartan can contribute to preserve renal function in elderly neoplastic patients allowing a better excretion of water-soluble chemotherapic drugs and lowering the risk of drug toxicity.

Several studies have demonstrated the uricosuric and nephroprotective properties of losartan, in different kind of patients also transplanted treated with Ciclosporine A (Mackenzie and Brenner,

1998; Hillebrand et al., 2002). None of these trials studied elderly, hypertensive, neoplastic patients treated with chemotherapy. Losartan has a good tolerability, an excellent antihypertensive efficacy and an effective uricosuric and nephroprotective effects; so it can be considered a first choice drug to use in hypertensive and hyperuricemic elderly patient. The findings of the present study support the effective role of losartan compared to amlodipine in treating hypertensive elderly patients under chemotherapeutic procedures.

Conflict of interest statement

None.

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