Preventive Effects of Renin-Angiotensin System Inhibitors on Oxaliplatin-induced Peripheral Neuropathy: A Retrospective Observational Study

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ABSTRACT

Purpose: Oxaliplatin-induced peripheral neuropathy has remained an unresolved issue in clinical practice. Our previous study hypothesized that inhibition of the renin-angiotensin system (RAS) may produce a preventive effect on oxaliplatin-induced neuropathy. The aim of this study was to clarify whether RAS inhibitors prevent oxaliplatin-induced peripheral neuropathy.

Methods: This study retrospectively analyzed data from cancer patients who had received chemotherapy including oxaliplatin and were treated with or without RAS inhibitors. This retrospective observational study was conducted at Ehime University Hospital using electronic medical records from May 2009 to December 2016. The primary end point was the incidence of severe peripheral neuropathy during or after oxaliplatin treatment, according to the Common Terminology Criteria for Adverse Events, version 4.0. A multivariate Cox proportional hazards model analysis was used to identify risk factors.

Findings: A total of 150 patients were included in the study. The estimated incidence of peripheral neuropathy was 36.9% and 91.7% in the RAS inhibitor group and the non−RAS inhibitor group, respectively. The multivariate analysis using a Cox proportional hazards model showed that the RAS inhibitor group was slightly associated with a decreased risk of neurotoxicity (adjusted hazard ratio, 0.42 [95% CI, 0.18−0.99]; $P = 0.048$).

Implications: The present findings suggest that RAS inhibitors have the ability to prevent oxaliplatin-induced peripheral neuropathy. (*Clin Ther.* 2018;■:1−10) © 2018 Elsevier Inc. All rights reserved.

Key words: angiotensin-converting enzyme inhibitor, angiotensin receptor blocker, chemotherapy-induced peripheral neuropathy, oxaliplatin, renin-angiotensin system inhibitors.

INTRODUCTION

Oxaliplatin, a third-generation platinum agent, is a key drug for chemotherapy in patients with colorectal, pancreatic, and gastric cancer. Several pivotal Phase III trials have found that oxaliplatin-based regimens are markedly superior to the previous regimens in prolonging the survival rate and improving the quality of life of cancer patients.[1−7] However, the major toxicity

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and/or adverse reactions induced by oxaliplatin include severe chronic neurotoxicity, which is observed in 44% to 50% of patients and also impairs the patients' quality of life.[8,9]

In the American Society of Clinical Oncology guideline, the antidepressant duloxetine is recommended for only pain treatment, but not prophylaxis, of chemotherapy-induced peripheral neuropathy (CIPN) caused by taxanes and platinum-based chemotherapy.[10] On the other hand, recent clinical studies have shown that administration of calcium gluconate and magnesium sulfate before and after oxaliplatin treatment and Goshajinkigan (a traditional Japanese herbal medicine), pregabalin, antihyperalgesic drugs, venlafaxine, and vitamin E had no significant preventive effect on oxaliplatin-induced neuropathy.[11–15] Conversely, the administration of Goshajinkigan for ≥4 weeks, both from the beginning of chemotherapy and from the middle of chemotherapy, may improve oxaliplatin-induced neuropathy and reduce the duration of continuing peripheral neuropathy.[16] However, oxaliplatin-induced peripheral neuropathy has remained an unresolved issue in clinical practice, and there have been no reports, to date, elucidating how to treat or prevent it.

Our previous study showed that coadministration of losartan (an angiotensin II type 1 receptor blocker [ARB]) and angiotensin II significantly increased the phenol-induced reduction of the density of CGRPergic nerves.[17] Furthermore, we also reported that hyperinsulinemia in an insulin resistance model (ie, fructose-drinking rats) played a pivotal role in the onset and/or development of hypertension that was caused by significantly decreased innervation of CGRPergic nerves and increased innervation of adrenergic nerves.[18,19] In addition, the treatment of fructose-drinking rats with ARB markedly ameliorated the decreased neurite elongation in dorsal root ganglia (DRG) cells, which are the cell bodies of CGRPergic nerves.[20] Conversely, the accumulation of oxaliplatin inhibited cellular metabolism and axoplasmic transport in sensory nerve cell bodies of DRG, resulting in damage to the peripheral nervous system. This process is the most widely accepted mechanism of oxaliplatin-induced persistent peripheral neuropathy.[21] It is expected that inhibition of the renin-angiotensin system (RAS) may produce a preventive effect on oxaliplatin-induced neuropathy. The present study was therefore designed to clarify whether RAS inhibitors have the ability to prevent oxaliplatin-induced peripheral neuropathy.

PATIENTS AND METHODS

Study Design

This retrospective observational study was conducted at Ehime University Hospital using data from electronic medical records of adult cancer patients (aged ≥20 years) who received >1 cycle of an oxaliplatin-based regimen from May 2009 to December 2016. Patient records were de-identified and analyzed anonymously. We extracted the necessary clinical information on patient demographic characteristics, including: age; sex; body mass index (BMI); body surface area; comorbidity of diabetes mellitus, shingles, and autoimmune disease; cancer type; previous chemotherapy; regimen, dose, and cycle of oxaliplatin; estimated glomerular filtration rate at baseline; regular use of concomitant drugs with RAS inhibitors; supportive therapies such as Goshajinkigan, vitamin B12, or pregabalin; calcium channel blockers; neurotoxicity-masked drugs such as opioids, NSAIDs, and antiepileptic drugs; antidepressants; and oxaliplatin-induced peripheral neuropathy. In this study, we defined the regular use of concomitant drugs to be oral intake of the drugs every day before the event of oxaliplatin-induced peripheral neuropathy during the study period, and that comorbidity of diabetes mellitus, shingles, and autoimmune disease meant a medical history of or current diagnosis of these diseases. Pharmacists in hospitals and community pharmacies routinely confirmed the compliance of oral medicines.

Subjects meeting any of the following criteria were excluded from the study: (1) participation in other clinical trials; (2) medical history of oxaliplatin-based regimens; (3) hospital transfer; (4) preexisting or current neurotoxicity, except for oxaliplatin-associated neuropathy, of any grade; (5) unknown evaluation of oxaliplatin-associated neuropathy; and (6) death within 1 month after oxaliplatin administration. We determined whether there was an onset of oxaliplatin-induced peripheral neuropathy after the administration of oxaliplatin.

The study protocol was approved by the ethics committee of Ehime University Hospital (approval number 1702010) and was conducted in accordance with the Declaration of Helsinki and the Ethical Guidelines for Medical and Health Research Involving Human Subjects by the Ministry of Education, Culture, Sports, Science, and Technology, and the Ministry of Health, Labour, and Welfare of Japan. Japanese law does not require individual informed consent from participants