Case Report

The efficacy of ogikeishigomotsuto on chronic cumulative sensory neuropathy induced by Oxaliplatin -Case report and Literature view-

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Abstract

Oxaliplatin (L-OHP) in combination with infusional 5-fluorourasil / Leucovorin (FOLFOX) has emerged as the treatment of choice for advanced, recurrent colorectal cancer, and its dose-limiting adverse effect is sensory neurotoxicity. We administered ogikeishigomotsuto (OKG: traditional herbal medicine, Kampo) to a patient with recurrence colon cancer with modified FOLFOX6(mFOLFOX6), who subsequently demonstrated clinical improvement of L-OHP-induced neuropathy.

A 59-year-old man with recurrent colon cancer was administered mFOLFOX6. During cycles 4, he complained of paresthesia in the distal extremities, which had been induced by L-OHP. To reduce the neurotoxicity of L-OHP, OKG was administered together along with the anticancer agents starting the 7th cycle. The severities of neurotoxicity before and after administration OKG were grade 2 and grade 1 based on the neurotoxicity criteria of DEBIOPHARM (DEB-NTC), respectively. This observation suggests that OKG may be useful agent to reduce or prevent chronic cumulative neurotoxicity due to L-OHP.

Key words ogikeishigomotsuto, Oxaliplatin, neuropathy, Kampo.

Introduction

Oxaliplatin (L-OHP) is one of the key drugs against advanced, recurrent colorectal cancer, and the FOLFOX regimen, which is a combination of l-leucovorin (l-LV) and 5-fluorouracil (5-FU) with L-OHP, is a standard therapy.\(^1\) Neurotoxicity is the most frequent dose-limiting toxicity of L-OHP and can manifest as either of two distinct syndromes: a transient, acute syndrome that can appear during or shortly after infusion, and a dose-limiting, chronic cumulative sensory neuropathy.\(^1\)

The current recommendations for the management of acute and cumulative neurotoxicity from L-OHP include education about exposure to cold, dose modification, “stop and go”,\(^2\) and the administration of neuromodulatory agents,\(^3-7\) in particular, intravenous Ca and Mg infusion. In Japan, traditional herbal medicine (THM), so-called Kampo, has also been used as therapy for L-OHP-related neurotoxicity. It has been reported that Ginkgo Biloba extract (GB),\(^8\) and goshajinkigan (GJG),\(^9,10\) which is a Kampo formula composed of 10 herbs, have prevented L-OHP-related neurotoxicity. However, it remains difficult for physicians to control this neuropathy.

In this report, we present a patient, who was successfully treated with ogikeishigomotsuto (OKG), which is another Kampo formula, for L-OHP-induced peripheral neuropathy in patients with metastatic colorectal cancer treated with the mFOLFOX6 regimen.

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Case report

A 59-year-old man was referred to a local hospital for evaluation after a positive fecal occult-blood test in February 200X-1. Colonoscopy was performed and an irregularity of the colonic wall at the ascending colon was detected. Biopsy specimens showed moderate differentiated tubular adenocarcinoma. He was referred to Gunma University Hospital for surgery. He underwent a right hemicolectomy and intraoperative diagnosis was ascending colon cancer (Stage IIIb). As adjuvant chemotherapy capecitabine at a dose of 2100 mg twice daily on days 1 through 14 every 21 days, was started. In October 200X-1, CT image for postsurgical surveillance indicated para-aortic lymph node swelling, and then colon cancer recurrence was diagnosed. As shown in Fig.1, modified FOLFOX6 (mFOLFOX6: Leucovorin 200 mg/m² iv 2 hrs before 5-FU day 1, 5-FU 400 mg/m² iv bolus day 1 followed by 2400 mg/m² iv 46 hrs, L-OHP 85 mg/m² iv day 1, Every 2 weeks) was started.

During cycles 4 in November, he complained of paresthesia in the distal extremities. During cycle 5, the symptom persisted between cycles, but did not cause any functional impairment (Grade 2 based on the neurotoxicity criteria of DEBIOPHARM (DEB-NTC)).

During cycle 7 in January 200X, he consulted a specialist in Japanese Oriental medicine to undergo treatment with THM for the paresthesia. His symptom was diagnosed as L-OHP-induced neuropathy, because he had no history of diabetes mellitus, heavy drinking, use of organic solvents or heavy metal. There were no apparent abnormalities in liver, kidney and thyroid function on blood analysis. For paresthesia, OKG extract (Table 1) was prescribed, because his symptom indicated KI-deficiency and deficiency of blood. Four weeks later, the intensity and duration in neuropathy was decreased (Grade 1 based on DEB-NTC), as a result, chemotherapy (11th cycle of mFOLFOX6) could be carried out without discontinuation (Fig.1).

<table>
<thead>
<tr>
<th>Japanese name</th>
<th>English common name</th>
<th>Botanical name</th>
<th>Dose(g)</th>
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<tbody>
<tr>
<td>Ogi</td>
<td>Astragal Radix</td>
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<td>Shakuyaku</td>
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<tr>
<td>Taiso</td>
<td>Zizyphi Fructus</td>
<td>Zizyphus jujuba Miller var. inermis Rehder</td>
<td>3</td>
</tr>
<tr>
<td>Shokyo</td>
<td>Zingiberis Rhizoma</td>
<td>Zingiber officinale Roscoe</td>
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The dose is indicated by the weight of each herb administered in this case.

![Diagram of mFOLFOX6 and Neurotoxicity](image)

**Fig. 1** Clinical course after treatment of mFOLFOX6
mFOLFOX6: modified FOLFOX6, Leucovorin 200 mg/m² iv 2 hrs before 5-FU day 1, 5-FU 400 mg/m² iv bolus day 1 followed by 2400 mg/m² iv 46 hrs, Oxaliplatin 85 mg/m² iv day 1, Every 2 weeks.
Discussion

Current progress in chemotherapy for colorectal cancer has improved patient prognosis.\(^1\) FOLFOX, a regimen containing L-OHP, has become the standard therapy for advanced colorectal cancer,\(^1\) making L-OHP-induced peripheral neuropathy a growing problem.\(^2\)

Neurotoxicity seen with L-OHP can manifest as either of two distinct syndromes\(^2\): a transient, acute syndrome or a cumulative sensory neuropathy. Acute, transient neurotoxicity occurs in nearly all patients. This toxicity is rapid in onset, occurring during or within a few hours of infusion. In contrast, chronic cumulative neuropathy symptoms generally persist between cycles and increase in intensity with cumulative dose. Impaired sensation, sensory ataxia, and/or deficit in fine sensory-motor coordination may ultimately occur\(^2\) and the symptoms may become severe enough to limit activities of daily living. In this case, the paresthesia persisted between cycles and therefore, we considered the symptoms such as numbness to have been derived from chronic cumulative neuropathy.

To control the symptoms by L-OHP-induced peripheral neuropathy, neuromodulatory agents, e.g. Ca/Mg infusion,\(^6\) Glutathione,\(^5\) Carbamazepine\(^6\) and Amifostine,\(^7\) have been tried. In Japan, THM (Kampo) has also used to select therapeutic agents for L-OHP-related neurotoxicity. Table 2 shows the list of treatment for chemotherapy-related neuropathy with THM. Marshall et al. demonstrated that GB decreased the intensity and duration of acute dysesthesia caused by L-OHP based on a retrospective analysis of 17 patients.\(^8\)

Kampo formula was also used as therapy for L-OHP-related neurotoxicity.\(^9\) It has been reported that GJJ prevented L-OHP-related neurotoxicity in patients with metastatic colorectal cancer treated with a FOLFOX4 regimen. Although L-OHP-induced neuropathy appeared in 10 patients among the 14 patients treated with GJJ, symptoms such as numbness showed a lower grade, namely grade 1 (n=7, 50%), grade 2 (n=3, 21.4%), grade3 (n=0). This observation suggests that the administration of GJJ improves L-OHP-related neurotoxicity.\(^10\) In addition, another researcher reported that treatment with GJJ resulted in the clinical improvement chemotherapy-induced neurotoxicity by L-OHP, as well as paclitaxel.\(^11\) It has been also reported that OKG prevented and reduced the occurrence and intensity of acute peripheral neuro-sensory toxicity caused by L-OHP.\(^15\) The present case was successfully treated with OKG for the chronic cumulative toxicity of L-OHP and suggested that OKG might be useful agent to reduce or prevent chronic cumulative neurotoxicity as well as acute neurotoxicity which induced by L-OHP.

OKG consists of 5 herbal drugs (Table 1), and has previously been used to treat patients with disturbance of perception, motoric paralysis and pruritus in Japan.\(^13,14\) Recent reports have shown successful treatments with OKG for symptoms of neuropathic diseases such as SMON (subacute myelo-optico-neuropathy),\(^16\) post herpetic neuralgia,\(^17\) spondylosis deformans\(^18\) and ANCA (Anti-neutrophil cytoplasmic antibody)-associated vasculitis.\(^19\)

While these mechanisms have remained unclear, it is considered that Ogi may be a key herb in OKG. Astragaloside IV (AGS-IV), which is one of the main

<table>
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<th>Author</th>
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<td>Li Y, 2006</td>
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<td>Oxaliplatin</td>
<td>goshajinkigan</td>
<td>9)</td>
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<td>goshajinkigan</td>
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<tr>
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<td>Paclitaxel</td>
<td>goshajinkigan</td>
<td>14)</td>
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<td>case report</td>
<td>Oxaliplatin</td>
<td>ogikeishigomotsuto</td>
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THM: traditional herbal medicine
ingredients isolated from Ogi, is a glycoside of cycloartenol-type triterpene. It has been reported that AGS-IV prevented the progression of peripheral neuropathy in STZ-induced diabetic rats.\(^{19}\) The protective action of AGS-IV on the progression of peripheral neuropathy involved direct effects on the nerves as well as improved glycemic control. As for the former mechanism, it has been demonstrated that AGS-IV increased the activity of glutathione peroxidase, which protects neurons from oxidative damage, and elevates Na\(^+\),K\(^+\)-ATPase activity in the nerves,\(^{20}\) which is decreased by a hyperglycemic state.

As for the pathogenesis of L-OHP-induced neuropathy, the acute sensory neuropathy seen with L-OHP is described in the literature as Na channelopathy\(^{21}\): the theory that an oxalate, which released intracellularly from L-OHP, affects the Na channels has been entertained by researchers. In contrast, the chronic cumulative toxicity of L-OHP appears to be related to direct toxicity to the nerve, unlike acute transient neuropathy.\(^{22}\) Importantly, AGS-IV protects nerves against peripheral neuropathy through the increment of glutathione peroxidase activity in rat model,\(^{23}\) which may protect against chronic cumulative toxicity induced by anti-cancer agents in humans.\(^{23}\) This protective effect of AGS-IV might, partially, explain how OKG improved the neuropathy symptoms induced by L-OHP in our patient. However, OKG is a crude drug containing several other chemical components. It is possible that these components may be the source of the neuroprotective effect. To identify the overall function of OKG, further clinical and pharmacological studies will be required.

In this study, we present a patient successfully treated with OKG, which is a Kampo formula, for L-OHP-induced peripheral neuropathy in patients with metastatic colorectal cancer treated with mFOLFOX6 regimen. Thus, it would be clinically significant to perform controlled trials to evaluate the clinical efficacy of OKG for L-OHP-induced neuropathy.

References


9) Mamiya, N., Kono, T., Mamiya, K., Satomi, M., Chisato, N. and Ebisawa, Y.: A case of neurotoxicity reduced with Goshaginki-gan in modified FOLFOX6 chemo-


