Rhubarb Use in Patients Treated with Kampo Medicines—A Risk for Gastric Cancer?

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In vitro mutagenic effects have been reported for ingredients contained in rhubarb. Therefore, rhubarb (Rhei Rhizoma) as an anthranoid laxative could be associated with a risk of developing gastric cancer as well as colorectal cancer. We are not aware of any reports that have examined the relationship between the use of rhubarb and the development of gastric cancer. During the period between 1979 and 1999, we treated 14616 patients using various Kampo medicines, which sometimes contained rhubarb. In the present study, we determined whether patients, diagnosed with gastric cancer during the period between 1979 and 1999, had been administered rhubarb before the development of gastric cancer. Among the 10 enrolled patients, only 2 patients had been administered rhubarb before the development of gastric carcinoma. The other 8 patients had never received rhubarb before the development of gastric carcinoma. Rhubarb use may have little connection with the development of gastric cancer in practice, even if some ingredients in rhubarb have shown carcinogenic activity in experimental studies.

Key words—rhubarb; stomach neoplasm; mutagen; carcinogen; Rhei Rhizoma

INTRODUCTION

Recent experimental studies1–7 and a prospective cohort study8 have provided evidence that anthranoid use poses a possible risk for the development of colorectal cancer, whereas a prospective case control study in 20009 indicated that neither anthranoid laxative use nor melanosis coli were associated with any significant risk for the development of colorectal adenoma or carcinoma. Whether the use of anthranoid laxatives is related to the development of colorectal carcinoma remains controversial.10

In vitro mutagenic effects have been reported for emodin3,4 and chrysophanol2,5 contained in rhubarb. A carcinogenicity study in rodents given 1-hydroxyanthraquinone (HA) or a placebo showed that the group receiving HA had a significantly higher incidence of the large bowel, liver and stomach neoplasms than the placebo group.11 Therefore, rhubarb (Rhei Rhizoma) as an anthranoid laxative might be associated with a risk of developing gastric cancer as well as colorectal cancer. We are not aware of any reports that have examined the relationship between the use of rhubarb and the development of gastric cancer.

Our department, Japanese Oriental (Kampo) Medicine was established in 1979. During the period between 1979 and 1999, we treated 14616 patients using various Kampo medicines, which sometimes contained rhubarb. In the present study, we determined whether patients, diagnosed with gastric cancer during the period between 1979 and 1999, had been administered rhubarb before the development of gastric cancer.

PATIENTS AND METHODS

To identify patients with gastric cancer among those consulting our department between 1979 and 1999, we referred to the “Patient Registration System” in the university hospital. Exclusion criteria were as follows: patients who developed gastric cancer before the first administration of Kampo medicine, patients in whom the diagnosis of gastric carcinoma was not confirmed histopathologically. We enrolled all patients with gastric cancer after exclusion, and examined all prescriptions administered before the development of gastric cancer. In each patient, we determined whether rhubarb was administered before the development of gastric carcinoma. For patients who developed gastric carcinoma after administration of rhubarb, the daily dose and duration of rhubarb use and period since the last rhubarb-use until development of gastric cancer were examined.
Table 1. Patients Diagnosed with Gastric Cancer

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Sex</th>
<th>Location</th>
<th>Histology</th>
<th>Disease</th>
<th>First visit</th>
<th>Rhubarb use</th>
<th>Diagnosis of carcinoma</th>
<th>Rapid urease test</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>62</td>
<td>M</td>
<td>body</td>
<td>well</td>
<td>RA</td>
<td>May 1980</td>
<td>no</td>
<td>Sep 1983</td>
<td>ND</td>
</tr>
<tr>
<td>4</td>
<td>61</td>
<td>F</td>
<td>antrum</td>
<td>poor</td>
<td>RA</td>
<td>May 1984</td>
<td>no</td>
<td>Jan 1989</td>
<td>ND</td>
</tr>
<tr>
<td>5</td>
<td>63</td>
<td>M</td>
<td>antrum</td>
<td>well</td>
<td>RA</td>
<td>Nov 1984</td>
<td>no</td>
<td>Oct 1991</td>
<td>(–)</td>
</tr>
<tr>
<td>6</td>
<td>72</td>
<td>M</td>
<td>antrum</td>
<td>well</td>
<td>Asthma</td>
<td>May 1985</td>
<td>no</td>
<td>Feb 1992</td>
<td>(–)</td>
</tr>
<tr>
<td>7</td>
<td>69</td>
<td>M</td>
<td>antrum</td>
<td>well</td>
<td>tinnitus</td>
<td>Jan 1986</td>
<td>no</td>
<td>Jan 1993</td>
<td>ND</td>
</tr>
<tr>
<td>8</td>
<td>77</td>
<td>F</td>
<td>antrum</td>
<td>well</td>
<td>RA</td>
<td>Mar 1986</td>
<td>no</td>
<td>Nov 1999</td>
<td>(+)</td>
</tr>
<tr>
<td>9</td>
<td>56</td>
<td>M</td>
<td>antrum</td>
<td>sig.</td>
<td>DM</td>
<td>Dec 1988</td>
<td>no</td>
<td>Mar 1993</td>
<td>ND</td>
</tr>
<tr>
<td>10</td>
<td>70</td>
<td>M</td>
<td>cardia</td>
<td>well</td>
<td>DM</td>
<td>Feb 1990</td>
<td>no</td>
<td>Feb 1999</td>
<td>ND</td>
</tr>
</tbody>
</table>


RESULTS

Among 14616 patients registered during the period between 1979 and 1999, 27 patients with gastric cancer were identified, and 17 patients out of 27 were excluded because they developed gastric carcinoma before administration of Kampo medicine. Among the 10 enrolled patients, only 2 patients had been administered rhubarb before the development of gastric carcinoma. Patient 1 (Table 1) was administered Teito-gan (daily rhubarb dose: 0.24 g) from June 1984 to March 1986 (for 21 months), and in August 1987 was diagnosed as having early gastric carcinoma (signet ring cell carcinoma). Patient 3 had been administered Daikan-gan (daily rhubarb dose: 1 g) from May 1983 to April 1985 (for 24 months), and diagnosed as having early gastric carcinoma (well-differentiated) in November 1990. The other 8 patients had never received rhubarb before the development of gastric carcinoma. Before the development of gastric cancer, each patient was administered 2 to 15 Kampo formulae which were revised occasionally as the disease progressed and as the body responded to Kampo therapy. These Kampo medicines varied and did not tend to favor any particular Kampo formulae. The rapid urease test for Helicobacter pylori was performed in only three patients out of 10, and was positive in one and negative in two patients.

DISCUSSION

Rhubarb is classified as an anthranoid laxative and is widely used in Japan as an herbal component in Kampo formulae. In the field of Kampo medicines, rhubarb (Rhei Rhizoma) is not only used as a laxative but also used to treat several other symptoms and diseases. Although anthranoid laxatives are recommended for short-term use only, Kampo formulae containing rhubarb are sometimes used for prolonged periods to treat patients with chronic diseases such as chronic renal failure. Thus, whether the use of rhubarb is related to the development of gastric cancer is a great difference among patients treated with Kampo medicines containing rhubarb.

In the present study, 10 patients who developed gastric carcinoma after administration of Kampo medicine were selected from 14616 patients. The incidence (10 to 14616) is not high compared with the incidence of gastric cancer in Japan: it is reported that gastric cancer develops in 5% of 1603 consecutive patients over 10 years. In the 10 enrolled patients, only two had been administered rhubarb before the development of gastric carcinoma. Recent studies have found that Helicobacter pylori is associated with gastric cancer. Particularly, Uemura et al. demonstrated that Helicobacter pylori chiefly affect the development of gastric cancer in Japanese people. In that prospective study, gastric cancer developed in persons infected with Helicobacter pylori but not in uninfected persons. Based on those findings together with our results, rhubarb use may have little connection with the development of gastric cancer in practice, even if some ingredients in rhubarb have shown carcinogenic activity in experimental studies.
but offered a useful suggestion on the practical use of rhubarb contained in Kampo medicine. Lack of a correlation between rhubarb use and the development of gastric cancer should be confirmed in a larger population using a well-designed protocol as performed in studies that examine the risk of stimulant laxative use for the development of colorectal cancer.

REFERENCES