

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 emodin^{3,4)} and chrysophanol^{2,5)} 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.

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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

Patient	Age	Sex	Location	Histology	Disease	First visit	Rhubarb use	Diagnosis of carcinoma	Rapid urease test
1	55	F	angle	sig.	RA	Apr 1980	May 1984–Mar 1986	Aug 1987	ND
2	62	M	body	well	RA	May 1980	no	Sep 1983	ND
3	75	F	cardia	well	bronchitis	Nov 1981	Jan 1983–Oct 1985	Nov 1990	ND
4	61	F	antrum	poor	RA	May 1984	no	Jan 1989	ND
5	63	M	antrum	well	RA	Nov 1984	no	Oct 1991	(–)
6	72	M	antrum	well	Asthma	May 1985	no	Feb 1992	(–)
7	69	M	antrum	well	tinnitus	Jan 1986	no	Jun 1993	ND
8	77	F	antrum	well	RA	Mar 1986	no	Nov 1999	(+)
9	56	M	antrum	sig.	DM	Dec 1988	no	Mar 1993	ND
10	70	M	cardia	well	DM	Feb 1990	no	Feb 1999	ND

sig.: signet ring cell carcinoma, well: well differentiated adenocarcinoma, poor: poorly differentiated adenocarcinoma, RA: rheumatoid arthritis, DM: diabetes mellitus, ND: not done.

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.¹²⁾ Although anthranoid laxatives are recommended for short-term use only,¹⁰⁾ Kampo formulae containing rhubarb are sometimes used for prolonged periods to treat patients with chronic diseases such as chronic renal failure.^{12,13)} 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.¹⁴⁾ 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.^{15,16)} Particularly, Uemura et al.¹⁴⁾ 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.^{1-7),11)}

The present study without control could not directly evaluate the risk of rhubarb use for gastric cancer,

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.

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