Modulation of Cancer Chemotherapy by Green Tea

Yasuyuki Sadzuka, Tomomi Sugiyama, and Sadao Hirota
School of Pharmaceutical Sciences, University of Shizuoka, Shizuoka 422, Japan

ABSTRACT
Biochemical modulation has played an important role in the development of cancer chemotherapy. We have directed our attention to the intake of common beverages and investigated the effects of green tea and tea components on the antitumor activity of doxorubicin. We carried out the combined treatment of doxorubicin and green tea on Ehrlich ascites carcinoma tumor-bearing mice. The oral administration of green tea enhanced 2.5-fold the inhibitory effects of doxorubicin on tumor growth. The doxorubicin concentration in the tumor was increased by the combination of green tea with doxorubicin. In contrast, the increase in doxorubicin concentration was not observed in normal tissues after green tea combination. Furthermore, the enhancement of antitumor activity of doxorubicin induced by green tea was observed in M5076 ovarian sarcoma, which has low sensitivity to doxorubicin. These results suggest that drinking green tea can encourage cancer chemotherapy and may improve the quality of life of clinical patients.

INTRODUCTION
In cancer chemotherapy, biochemical modulation has been studied extensively (1–4), and the enhancements of the activity of antitumor drugs, e.g., 5-fluorouracil (3, 4), are confirmed in clinical treatments. However, when the modulators induce the enhancement of antitumor effects, the examination of its side effects are not enough, and there are some cases of patients dying as the result of biochemical modulation. The development of a new modulator, which enhances antitumor activity and reduces the side effects of antitumor agents, has been needed. In addition, the use of modulators increases the number of medications and adds to the patient’s burden. Simultaneously, the study to improve the quality of life of patients is also necessary. If the intake of food or beverage as modulator enhances antitumor activity (biochemical modulation), then the improved antitumor activity by this type of biochemical modulation will reduce the patient’s burden.

We have directed our attention to Japanese green tea (Camellia sinensis), one of the common beverages that has been popular in Japan and China for a long time. Some green tea components have been reported to have useful effects (5–9), and the interest in these evaluations is high. Green tea inhibits carcinogenesis and is known to be effective for the chemoprevention of cancer (8, 9). However, the effects of green tea on cancer chemotherapy have never been investigated previously. Frequently, drinking green tea, coffee, or black tea is restricted for clinical patients. These restrictions may hinder the mental stability of the patients and/or occasionally have a bad influence on the therapy. If green tea has a positive action on cancer chemotherapy, we could expect that cancer therapy would become more effective and that the patient’s mental condition would become better by drinking green tea as usual.

To examine the effects of the oral administration of green tea on cancer chemotherapy, we have performed animal experiments, designed to consider the effects of drinking green tea during clinical treatment. In this study, we investigated the combination of green tea with DOX, an antitumor antibiotic widely used in clinical therapy (10–12), on tumor-bearing mice. The effects of theanine and caffeine, which are known to enhance the activity of antitumor agents (13–16), as green tea components (5), were examined as well.

MATERIALS AND METHODS

Chemicals. DOX injection, 10 mg/vial (Adriacin®), was purchased from Kyowa Fermentation, Inc. (Tokyo, Japan). Theanine was purchased from Tokyo Kasei Co., Ltd. (Tokyo, Japan). Caffeine was purchased from Wako Pure Chemical Industries, Ltd. Green tea powder was a product of Shizuoka (Shizuoka, Japan). The drugs were dissolved in sterile isotonic saline. The other chemicals used in this study were of the highest purity available.

Animals. Male CDF1 and BDF1 strain mice, 5 weeks of age and 20–25 g, were obtained from Japan SLC, Inc. (Hamamatsu, Japan). The animals were housed in a room maintained at 25 ± 1°C with 55 ± 5% relative humidity and were given free access to regular chow pellets (MF, Oriental Co., Ltd., Tokyo, Japan) and water.

Tumors. Ehrlich ascites carcinoma (1 × 10⁶ cells/animal) were i.p. transplanted into the CDF1 mice. The ascites were collected on the 7th day after transplantation. M5076 ovarian sarcoma was kindly provided by Dr. T. Tashiro (Japanese Foundation for Cancer Research, Tokyo, Japan).

Animal Experiments. Ehrlich ascites carcinoma (5 × 10⁵ cells/animal) were transplanted onto the backs of CDF1 mice. DOX (2.0 mg/kg/day for 4 days) was i.p. administered on the 10th, 12th, 14th, and 16th days after transplantation. Green tea powder (1.0 g/kg/day for 4 days) and theanine and caffeine...
Table 1

<table>
<thead>
<tr>
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<th>Control</th>
<th>DOX</th>
<th>p.o.</th>
<th>i.p.</th>
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<tr>
<td>Tumor weight</td>
<td>100</td>
<td>80</td>
<td>60</td>
<td>50</td>
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Fig. 1 Effects of green tea and tea components on the changes in tumor weight (Ehrlich) induced by DOX. Each column is the mean of eight mice expressed as percentage of control level; bars, SD. Significant differences from the level of the DOX-alone group are indicated by: a) \( P < 0.001 \); b) \( P < 0.01 \); and c) \( P < 0.05 \).

Fig. 2 Effects of test drug on the DOX concentration in the tumors of mice. Each point is the mean of eight mice; bars, SD. Significant difference from the level of the DOX-alone group is indicated by: a) \( P < 0.001 \).

Green tea combined with DOX increased the DOX concentration by 1.7-fold compared to the DOX-alone group. DOX did not increase the DOX concentration in the heart and liver of tumor-bearing mice. In particular, the combination of theanine and DOX reduced the DOX concentrations in the heart \( (P < 0.05) \).

**Figures and Tables**

**DISCUSSION**

Oral administration of green tea was combined with DOX treatment on Ehrlich solid tumor-bearing mice. Tumor growth was inhibited by DOX, and the administration of DOX alone decreased the tumor weight by 25\% compared with the control level, whereas the addition of green tea remarkably reduced the tumor weight to 37\% of the control level and significantly enhanced by 2.5-fold the DOX inhibitory effect on tumor growth. This result indicates that drinking green tea causes the enhanced activity of antitumor agents. This effect of green tea is new evidence and provides the possibility that green tea acts as a biochemical modulator. We may expect that green tea promotes cancer chemotherapy. Similarly, the enhancement of the antitumor activity of DOX was observed by the i.p. and oral administration of theanine or caffeine with DOX. Thus, theanine and caffeine were indicated to be effective as biochemical modulators, and it is suggested that the effect of green tea depends on these components.

We determined the DOX concentration in the tumor, as the targeted tissue, and in normal tissues. The DOX concentration in the tumor was significantly increased by the combination of green tea or tea components with DOX compared with the DOX alone group. This increment of DOX concentration in the tumor was regarded as the direct cause of the enhancement of antitumor activity, induced by green tea or tea components. In previous reports (13, 14), we have confirmed that theanine and caffeine increased the DOX concentration by 2.2-fold \( (P < 0.001) \).
against which DOX was not effective, an antitumor effect of tea enhanced the antitumor activity of DOX against M5076. Thus, these results demonstrate that green theanine, with DOX significantly decreased the tumor weight to 55% of control level. In contrast, the combination of green tea, we examined these effects on M5076 ovarian sarcoma (22), with DOX alone. In contrast, the combination of green tea, with DOX significantly decreased the tumor weight to 55% of control level. Thus, these results demonstrate that green tea reduces the lipid peroxide level. Thus, we can expect that green tea may reduce the side effects of DOX from the point of view of drug distribution.

Cardiac toxicity is very severe side effect of DOX and is reported to be caused by the elevation of lipid peroxide in the heart (12, 17, 18). Because green tea has some antioxidative components, e.g., catechins (5, 19–21), we could expect that drinking green tea reduces the lipid peroxide level. Thus, we can expect that drinking green tea reduces the cardiac toxicity induced by DOX because of a decrease in the lipid peroxide level in the heart as well as the DOX concentration.

Many studies about biochemical modulation were not performed in the past in consideration of both the antitumor effects and side effects of a drug, whereas green tea described in this study can be an ideal biochemical modulator because it has beneficial effects on both the antitumor activity and side effects of antitumor agents. Because green tea is a common beverage, the combination of drinking green tea with chemotherapy is easy to try for humans in clinical treatment. We expect that cancer chemotherapy with the addition of green tea will induce a positive effect.

Furthermore, to investigate the broad usefulness of green tea, we examined these effects on M5076 ovarian sarcoma (22), which has low sensitivity to DOX. The inhibitory effect on M5076 tumor growth was not observed by the administration of DOX alone. In contrast, the combination of green tea, as well as theanine, with DOX significantly decreased the tumor weight to 55% of control level. Thus, these results demonstrate that green tea enhanced the antitumor activity of DOX against M5076 tumor, indicating that the effects of green tea as a modulator are not specific to Ehrlich ascites carcinoma. On the M5076 tumor, against which DOX was not effective, an antitumor effect of DOX was observed with the addition of green tea, without elevating the dose of DOX. Therefore, we may expect similar enhancement of antitumor effects by green tea against tumors of low sensitivity or drug-resistant tumors. These results suggest that green tea has a very important effect on cancer chemotherapy.

In this study, drinking green tea was demonstrated to enhance the antitumor activity and to reduce the side effects of DOX. We found that green tea has physiological effects as a biochemical modulator as well. For patients in clinical treatment with antitumor agents, it is easy to suggest drinking green tea with a meal. Green tea may have positive influences on cancer chemotherapy. We think that the intake of a favorite beverage favors a patient’s positive mental attitude and encourages the efficiency of the chemotherapeutic index, and that this efficacy is useful in improving the quality of life in cancer chemotherapy. This discovery appears important in the field of study of biochemical modulation.

The fact that green tea is useful not only for cancer chemoprevention but also for encouraging the efficacy of chemotherapy may be good news for clinical patients. The results of this study may be helpful to promote the eradication of cancer in the future. We hope that clinicians encourage their patients to drink green tea, according to these results, so that cancer therapy will be more successful.

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<th>Group</th>
<th>Heart (ng/g tissue)</th>
<th>Liver (ng/g tissue)</th>
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<tbody>
<tr>
<td>DOX alone</td>
<td>464 ± 112</td>
<td>702 ± 232</td>
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<tr>
<td>DOX + green tea</td>
<td>376 ± 144</td>
<td>618 ± 166</td>
</tr>
<tr>
<td>DOX + theanine</td>
<td>224 ± 69</td>
<td>658 ± 65</td>
</tr>
<tr>
<td>DOX + caffeine</td>
<td>456 ± 152</td>
<td>716 ± 22</td>
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*Each value is the mean ± SD of eight mice.

*Significant difference from the level of the DOX-alone group: *P < 0.05.

**Table 1** Doxorubicin concentration in the heart and liver of mice

**Fig. 3** Effects of green tea and theanine on the changes in tumor weight (M5076) induced by DOX. Each column is the mean of eight mice expressed as percentage of control level; bars, SD. Significant differences from the level of the DOX-alone group are indicated by: a) *P < 0.01; and b) *P < 0.05.

REFERENCES

4. Bud, G. T., Fleming, R. M., Bukowski, R. M., McCracken, J. D., and Rinvik, S. E. 5-Fluorouracil and folinic acid in the treatment of...
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