The Effect of Lentinan Combination Therapy for Unresectable Advanced Gastric Cancer

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Abstract. *Background: Developed as a biological response modifier (BRM), lentinan mitigates patients' symptoms by boosting the immune system. In combination with S-1 (tegafur, gimeracil, oteracil), lentinan is reported to mitigate adverse reactions to therapy for unresectable recurrent gastric cancer and prolong survival. However, there are few reports from actual clinical practice, and precise methods of using lentinan have not yet been established. This study retrospectively examined the usefulness of lentinan in patients. Patients and Methods: The subjects of this study were 39 patients who were diagnosed with unresectable gastric cancer, based on preoperative examinations or findings at laparotomy in our Department. These patients underwent S-1/paclitaxel therapy. Nineteen of the patients received lentinan while 20 did not, and these two groups of patients were compared. Results: There were no significant differences in patients' characteristics such as the male:female ratio, age at the start of chemotherapy, and staging classification of the 19 patients receiving lentinan and the 20 patients not receiving lentinan. Comparison of the two groups revealed no significant differences in overall survival time, but comparison of the duration of therapy revealed that therapy tended to be longer for the group taking lentinan than the group not taking lentinan. Adverse events were noted in 61.5% (24 patients) of the total patients group; such events tended to occur less frequently in the group receiving lentinan. Conclusion: Lentinan inclusion in therapy did not seem to prolong survival. Nevertheless, the duration of therapy tended to be longer for patients taking lentinan. This may be due to the fact that adverse events tended to occur less frequently in these patients during therapy. A decline in the incidence of adverse events increases the duration of therapy and improves the patients' quality of life (QOL); it may also prolong survival. Optimal methods of using lentinan need to be established.*

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Chemotherapy is considered the first choice for the treatment of unresectable and recurrent gastric cancer. In recent years, chemotherapy including S-1 (tegafur, gimeracil, oteracil) has been reported to improve therapeutic outcomes (1-4). Drugs that are typically combined with S-1 are cisplatin, irinotecan, and taxane-based drugs. The combination of S-1 and paclitaxel is a regimen that is relatively safe with a high response rate (4, 5). A biological response modifier (BRM) is a drug or method that seeks to alter the host–tumor interaction by changing the host's responsiveness to tumor cells, therefore BRMs are expected to be of therapeutic benefit to some patients with cancer. Lentinan was developed as a BRM and is efficacious when combined with a tegafur preparation such as S-1.

As reported here, this study retrospectively examined the usefulness of therapy including lentinan in patients with unresectable advanced gastric cancer.

Patients and Methods

The subjects of this study were 39 patients who were diagnosed with unresectable gastric cancer based on preoperative examinations, such as computed tomographic scans, or perioperative findings at our Department from 2005 to 2010. These patients underwent S-1/paclitaxel therapy. Nineteen of the patients received lentinan, while 20 did not, and these patients were compared. For S-1/paclitaxel therapy, S-1 at 80-100 mg was administered orally for two weeks with a respite of one week; an infusion of paclitaxel (75 mg) was given on days 1 and 8. The group that was given lentinan was also given an infusion of lentinan at 2 mg on days 1 and 8.

Table I. *Patients' background characteristics.*

	With lentinan (n=19)	Without lentinan (n=20)	*p*-Value
Age, mean±SD, years	60.5±12.3	63.7±10.4	0.195
Male/female	10/9	11/9	0.882
*Stage IV	17	19	0.548
IIIA	1	1	
IIIB	1	0	

*TNM classification.

Table II. *Adverse events.*

	Lentinan therapy	
	With	Without
Hair loss	4	4
Leukopenia	2	6
Nausea	1	4
General fatigue	2	1
Numbness in the fingers	0	3
Diarrhea	1	1
Liver dysfunction	0	2
Fever	0	2
Loss of appetite	1	0
Stomatitis	0	2
Pigmentation	0	1
Taste abnormality	0	2
Respiratory discomfort	1	0
Vasculitis	0	1

Adverse events were observed in 24 cases (some had multiple events).

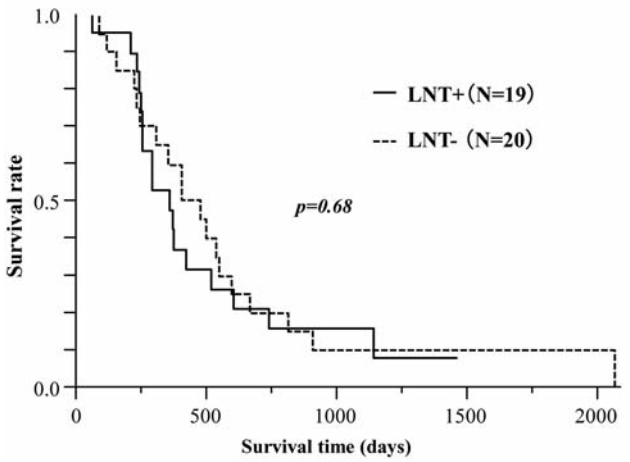

Figure 1. *The Kaplan-Meier curves for overall survival times of the two groups taking or not taking lentinan (LNT) are shown. Significant differences were not noted (p=0.68).*

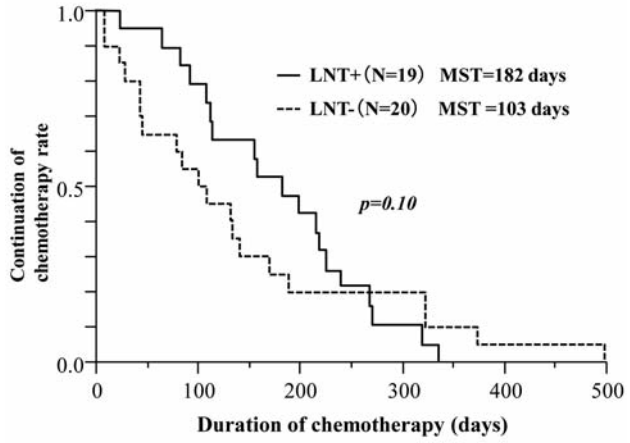

Figure 2. *The Kaplan-Meier curves for the rate of continued chemotherapy for the two groups taking or not taking lentinan (LNT) are shown. The duration of therapy tended to be longer for the group taking lentinan (p=0.10).*

Results

The male:female ratio for the 29 patients was 29:18, and the mean observation time was 16.6 (1.9-67.6) months. Patients' characteristics for the group receiving lentinan and the group not taking lentinan are shown in Table I; there were no significant differences between the two groups. Out of the 39 patients, three survived, while 36 died. Comparison of the survival rate for the group taking lentinan and the group not taking lentinan revealed no significant differences between the two groups (Figure 1). Comparison of the duration of therapy indicated a *p*-value of 0.10 and revealed no significant differences, but therapy tended to be longer for the group taking lentinan. Comparison revealed that the median duration of therapy was 182 days for the group taking lentinan *versus* 103 days for the group not taking lentinan. Therefore therapy was prolonged by 79 days for the group taking lentinan (Figure 2). During treatment, adverse events were noted in 24 out of the 39 patients (61.5%); details are shown in Table II. The group taking lentinan had less leukopenia and nausea. In addition, the group taking lentinan had fewer distressing events, such as numbness in the fingers, stomatitis, and dysgeusia during chemotherapy (Table II). Comparison of the number of the experienced adverse events revealed no significant differences, but the group taking lentinan tended to experience fewer adverse events (p=0.076) (Figure 3).

Discussion

Lentinan is purified from the hot water extract of *Lentinus edodes,* an edible mushroom in Japan (6). It is a macromolecular polysaccharide and its structure has been revealed (6, 7). Its triple-helix structure is considered to be

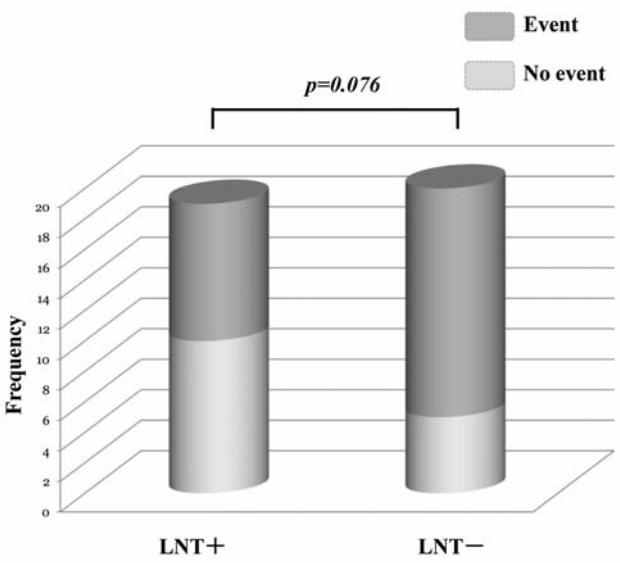

Figure 3. *The number of patients experiencing adverse events during therapy is shown. Twenty-four patients experienced adverse events (some had multiple events). The group taking lentinan (LNT) tended to have fewer adverse events (p=0.076).*

important in recognizing host cells (8). Lentinan acts by inducing antitumor effector cells, such as cytotoxic killer T–cells, natural killer cells, and activated macrophages in the host (7, 9-14). The antitumor action of lentinan has been noted in carcinomas transplanted in animals and autologous tumor cells (15-18). As a result of clinical trials, lentinan was approved as an anticancer agent in Japan, in 1985. Currently, lentinan is used in combination with a tegafur in order to sustain the treatment of inoperable, and recurrent gastric cancer (19-22).

The main thrust of current chemotherapy to treat unresectable advanced gastric cancer is multidrug therapy, which includes molecularly targeted treatment. Numerous comparative studies are being conducted to provide new evidence for the effect of therapy for unresectable advanced gastric cancer.

More than 25 years have passed since lentinan was first used. In clinical practice, patients undergoing chemotherapy that included lentinan, appear happier and more energetic during their visits than patients not receiving the agent. This study sought to verify that impression. Nutritional status, weight, white blood cell counts, tumor markers, and other factors were examined, but clear statistically significant differences were not noted. Adding lentinan to S-1/paclitaxel therapy is reported to limit the incidence of adverse reactions and improve quality of life (23). Similarly, the duration of therapy tended to be prolonged in the current study because the group taking lentinan tended to have fewer adverse events. Since lentinan resulted in fewer adverse events, it is probably suit for treatment of the elderly. In addition, lentinan has advantages in terms of health care economics, given the daunting costs of chemotherapy and therapy with molecularly targeted drugs.

In Japan, a phase III trial of therapy with S-1 alone and a combined therapy with S-1 and lentinan (JFMC36-0701) began in 2007, and the resulting data should be publicly available after June 2012. These results are eagerly anticipated.

Conclusion

Lentinan is a promising element of chemotherapy that should reduce adverse events during treatment and maintain good quality of life for longer periods of time. In the future, optimal methods of using lentinan should be studied.

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