Efficacy of Orally Administered Superfine Dispersed Lentinan (β-1,3-Glucan) for the Treatment of Advanced Colorectal Cancer

SHOICHI HAZAMA1, SEIJI WATANABE2, MANABU OHASHI3, MASASHI YAGI4, MICHINARI SUZUKI5, KENJI MATSUDA6, TATSUHITO YAMamoto7, YASUYO SUGA8, TETSUYA SUGA9, SABURO NAKAZAWA10 and MASAAKI OKA1

1Department of Surgery II, Yamaguchi University Graduate School of Medicine, 1-1-1 Minami-Kogushi, Ube, Yamaguchi; 2Chemotherapy Division, Inoue Hospital, Nishi 2-Chome, Minami 7-Jo, Chuo-Ku, Sapporo, Hokkaido; 3Digestive and General Surgery, Niigata University of Medicine, 1-754 Asahimachi-Dori, Chuo-Ku, Niigata; 4Department of Surgery, Public Central Hospital of Matto-Ishikawa, 3-8 Kuramitsu, Hakusan, Ishikawa; 5Department of Surgery, Shunan City Shinnanyo Hospital, 2-3-15 Miyanomae, Shunan, Yamaguchi; 6Hashimoto Hospital, 4-31 Minaminonocho, Horidome, Wakayama; 7Surgery Division, Iseikai Tsushima Hospital, 413-1 Emukai, Hagi, Yamaguchi; 8Pharmaceutical Laboratories, Ajinomoto Co., Inc., 1-I Suzuki-Cho, Kawasaki-Ku, Kawasaki, Kanagawa; 9Pharmaceutical Alliance Department, Ajinomoto Co., Inc., 2-1-1 Irifune, Chuo-Ku, Tokyo; 10Yamashita Hospital, 1-3-5 Nakamachi, Ichinomiya, Aichi, Japan

Abstract. Background: Lentinan (LNT) is an immune adjuvant medicine for advanced gastric cancer in Japan. Recently, an oral formulation of superfine dispersed lentinan (SDL) has become clinically available. To investigate the safety and effectiveness of SDL, a multicenter clinical study in patients with advanced colorectal cancer was conducted. Patients and Methods: Adverse events were assessed and the patients’ quality of life (QOL) and the binding ability of peripheral blood monocytes (PBM) to LNT were also evaluated. Results: Four grade 2 adverse events associated with SDL treatment were observed among the 80 patients. Adverse events associated with chemotherapy were observed in 9 out of the 64 chemotherapy-treated patients. Among the 48 patients assessed for QOL, the patients with low QOL scores before SDL treatment (n=23) reported a significant improvement in their QOL scores after 12 weeks of SDL administration. The rates of LNT-binding PBM in the QOL-improved group were significantly higher than those in the QOL-not-improved group (p<0.05). Conclusion: SDL was safe and effective for suppressing the adverse effects of chemotherapy as well as improving QOL. The binding ability of PBM to LNT appears to be a promising predictor of QOL improvement after SDL administration.

Lentinan (LNT) is a purified β-1,3-glucan with β-1,6-branches derived from the edible mushroom Lentinus edodes (Berk) Sing (1). LNT has immune adjuvant effects and has been reported to increase host defense mechanisms against murine and human tumors (2-4). The clinical efficacy of LNT, such as its effect on long-term survival and the improvement of the quality of life (QOL) status, were evaluated in patients with inoperable and recurrent gastric cancer (5, 6). The mode of action of LNT consists of T-cell-dependent immunopotentiation mediated by macrophages and monocytes (7-9). Studies of some β-glucan receptors such as CD11b, dectin-1 and toll-like receptor 2 (TLR2) have revealed that β-glucan binds to these receptors on macrophages and monocytes (10-12). Furthermore, LNT-induced reductive macrophages are reportedly skewed toward Th1 as a result of the production of IL-12 (13-15), and the binding ability of peripheral blood monocytes (PBM) to LNT might directly influence the balance between Th1 and Th2 (9). However, why orally administered LNT is ineffective has been a long-standing puzzle. In aqueous solution, the particle size of LNT is

0250-7005/2009 $2.00+.40

2611
approximately 100 to 200 μm; this impedes the absorption of LNT particles through the intestinal mucosa. Recently, an oral formulation of superfine dispersed lentinan (SDL) has been developed and is now clinically available. SDL reportedly enables the potentiation of intestinal mucosal immunity (17).

In the present study, we evaluated the safety and efficacy of SDL for suppressing the adverse effects of chemotherapy and the usability of the binding ability of peripheral blood CD14+ monocytes to LNT as a promising predictor of QOL improvement in patients with advanced colorectal cancer who have been treated with SDL.

Patients and Methods

Patients. Between July 2004 and April 2005, patients with unresectable colorectal cancer were enrolled at 25 centers involved in a study group on Foods and Lifestyle-related Disease, an affiliated organization of the Japanese Society of Geriatric Gastroenterology.

Eligibility. Patients who fulfilled the following eligibility requirements were enrolled in the study: (i) a diagnosis of unresectable colorectal cancer; (ii) an age of 20 years or older; (iii) an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of Grade 2 or lower; (iv) an ability to drink at least 100 ml of water per dose; (v) a life expectancy of at least 3 months; (vi) not receiving immunotherapy (the last immunotherapy session must have been completed at least 4 weeks before enrollment); (vii) not taking immune adjuvant foods (the last immune adjuvant food treatment must have been completed at least 2 weeks before enrollment); (viii) no allergies to Shiitake mushrooms (Lentinus edodes) or soybeans; (ix) adequate bone marrow function (hemoglobin concentration ≥10 mg/dl, white blood cell (WBC) count ≥3,000/μl and ≤12,000/μl, neutrophil count ≥1,500/μl and platelet count ≥10x10^9/μl); (x) adequate liver function (serum bilirubin levels, aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 times the upper limit of normal); (xi) adequate renal function (serum creatinine levels within normal limits); (xii) no other severe medical conditions; and (xiii) no other active malignancies. Written informed consent was obtained from all the patients. Pregnant women and patients receiving steroids or immunosuppressive medicines for a prolonged period were excluded from the study. This study was approved by the Institutional Review Boards at all the participating hospitals. The approvals were based on the 2000 revision of the Helsinki Declaration.

Test sample containing SDL. The SDL-containing test sample was supplied by Ajinomoto Co., Inc. and was prepared in 100 ml bags containing 15 mg of SDL per bag. According to the manufacturer’s specification, the mean particle diameter of the LNT was 0.08 μm (17). No change in the distribution of particle sizes was noted after 18 months of storage at room temperature. The oral superfine dispersed formulation was confirmed to enable the LNT to adhere onto or to be taken up into Peyer’s patches of the small intestine, and electron microscopy showed that the LNT particles were present in the vacuoles of epithelial cells (18). These results indicate that LNT was not taken up into the Peyer’s patches unless it was dispersed as superfine particles.

Treatment schedule. SDL was administered at a dose of 15 mg of LNT once daily for 12 weeks. During the period of SDL administration, the patients were also treated with various chemotherapy regimens, such as 5-fluourouracil (5-FU); tegafur and uracil (UFT); tegafur, gimeracil and oteracil potassium (S-1); doxifluoridine (5’-DFUR); levofolinate (LV); irinotecan (CPT-11); gemcitabine (GEM); or cisplatin (CDDP). Treatment was continued until disease progression, unacceptable toxicity, an adverse event, or the withdrawal of patient consent. Compliance was assessed using data obtained from scheduled interviews with the patients and regular monitoring.

Assessment of safety. A complete blood cell count, liver function tests, renal function tests and urinalysis were performed at least every 4 weeks throughout the study period. Adverse events were evaluated according to the CTCAE v3.0 (Common Terminology Criteria for Adverse Events version 3.0) (19).

Evaluation of QOL. QOL was evaluated using the QOL Questionnaire for Cancer Patients Treated with Anticancer Drugs (QOL-ACD) in 48 patients who were able to answer the questionnaire before and after 4, 8 and 12 weeks of SDL administration. The QOL-ACD was developed by Kurihara et al. in 1993 and is endorsed by the Japanese Ministry of Health, Labor and Welfare. The questionnaire is the first patient-assessed QOL evaluation system for Japanese cancer patients for which the reliability, validity and sensitivity to anticancer treatment have been verified (20). The QOL-ACD was primarily developed to assess outcome in clinical trials. Briefly, the QOL-ACD consists of 22 items, 21 of which are investigated using Likert scales covering four domains, namely, activity (6 items), physical (5 items), psychological (5 items) and social (5 items) aspects. The remaining item covers global aspects of QOL as represented by a face scale consisting of five different faces selected from the original ones used by Lorish and Maisak (21). Patients were invited to answer all questions by circling a number on the scale or the face that best described their state. The scores for all questions (1 to 5) were totaled to produce an overall QOL score ranging from a minimum of 22 to a maximum of 110. A higher score represents a higher QOL status.

Binding ability of CD14+ monocytes to LNT. Fluorescein-labeled LNT (F-LNT) was prepared using a reductive amination method (22). Briefly, the LNT solution plus 2 mM of sodium periodide was stirred at 4°C overnight and then ethylene glycol was added. The mixture was dialyzed with distilled water. Fluorescein 5-thiosemicarbazide (40 μg/ml; Molecular Probes, Eugene, OR, USA) was added under alkaline conditions and stirred at 4°C overnight. Schiff-bases were reduced using sodium borohydride. The resulting F-LNT was stored at 4°C under light shielding before use.

Peripheral blood (PB) samples were collected into tubes containing sodium heparin anticoagulant prior to the initiation of SDL administration. The PB was then incubated with F-LNT at 37°C for 75 minutes. During the last 30 minutes, phycoerythrin-labeled anti-CD14 antibody (CALTAG, Burlingame, CA, USA) was added. The erythrocytes were lysed with FACS Lysing Solution (Becton Dickinson, San Jose, CA, USA) for 10 minutes at room temperature. After washing with phosphate-buffered saline, the fluorescence intensity of the CD14+ monocytes was measured using a fluorescence-activated cell sorter (FACS Calibur; Becton Dickinson).

Statistical analysis. The QOL scores of the patients before and after SDL administration were compared using a Wilcoxon signed rank test.
The rates of LNT-binding PBM were compared using a Mann-Whitney U-test. P-values of less than 0.05 were considered statistically significant.

Results

Patient characteristics. The demographic characteristics of the patients are shown in Table I. Between July 2004 and April 2005, 80 patients with unresectable colorectal cancer were enrolled and treated with SDL. SDL-related adverse events were evaluated in all the patients. Three patients were later found to have had a low WBC count (<3,000/μl), a high WBC count (>12,000/μl), or a low hemoglobin concentration (<10.0 g/dl) prior to the start of SDL administration. Two patients were given a biological response modifier (BRM) within the SDL treatment period. Four patients became unable to drink at least 100 ml of water per dose within 2 weeks after enrollment.

The demographic characteristics of the patients are shown in Table I. Between July 2004 and April 2005, 80 patients with unresectable colorectal cancer were enrolled and treated with SDL. SDL-related adverse events were evaluated in all the patients. Three patients were later found to have had a low WBC count (<3,000/μl), a high WBC count (>12,000/μl), or a low hemoglobin concentration (<10.0 g/dl) prior to the start of SDL administration. Two patients were given a biological response modifier (BRM) within the SDL treatment period. Four patients became unable to drink at least 100 ml of water per dose within 2 weeks after enrollment.

Safety of SDL and adverse events during chemotherapy. Four adverse events (5%) that were or were suspected to have been related to SDL were observed within the period of SDL treatment: diarrhea occurred in 2 patients, and a rash and constipation occurred in 1 patient each. These events were grade 2 and disappeared or remitted within the study period.

As shown in Table II, chemotherapy-related adverse events were observed in 9 (14%) out of the 64 patients who received chemotherapy among the 71 patients who were eligible for inclusion in this study. Only one patient suffered from a grade 4 adverse event (neutropenia) after receiving 5-FU/LV chemotherapy. The other adverse events in the 8 patients were grade 1 or 2. Among patients who received a CPT-11-based or a 5-FU-based regimen, adverse events were observed in 5 (19%) out of 27 patients and 4 (11%) out of 37 patients, respectively. Among the 24 patients who were treated with a chemotherapy regimen containing S-1, only 1 (4%) patient exhibited an adverse event (grade 1).

Improvement of QOL status after SDL administration. Forty-eight patients received SDL everyday for 12 weeks and were able to answer the questionnaire both before and after 4, 8 and 12 weeks of SDL administration. The median overall QOL score before SDL administration was 85. Since no significant difference in the QOL scores was observed before and after the administration of SDL, the overall QOL scores tended to remain constant throughout the 12 weeks of administration (Figure 1A). Among these 48 patients, 23 patients had a QOL score that was less than 85 before the start of SDL administration (QOL low-score group). The QOL scores of this group improved significantly after 12 weeks of SDL administration. Figure 1B shows the changes in the overall QOL scores from before administration to after 12 weeks of SDL administration in the QOL low-score group (p=0.0199, Wilcoxon signed rank test). In 15 (65%) out of the 23 patients in the QOL low-score group, the overall QOL scores improved after 12 weeks of SDL administration.

Binding ability of CD14+ PBMs to LNT and its relation to QOL improvement. A histogram showing the results of a FACS for CD14+ PBMs is shown in Figure 2. Two types of PBMs were present: bright-positive cells (strong F-LNT binding) and dull-positive cells (weak F-LNT binding) cells. The binding ability of PBMs to LNT was measured before the initiation of SDL administration. The rates of bright-positive cells among the CD14+ PBMs varied individually, with a median of 3.6%, ranging from 0.2% to 44.4% among the 48 patients. The patients were divided into three categories: namely, a high (≥5.0%, n=20), moderate (1.0-4.9%, n=19) and low (<1.0%, n=9) group. Changes (Δ) in the overall QOL scores from before to after 12 weeks of SDL administration were then evaluated and the patients were divided into three groups, namely: an ‘improved’ (Δ>0, n=22), a ‘high-score maintained’ (Δ≤0 and QOL score at 12 weeks of SDL administration ≥85, n=12); and a ‘not-improved’ (Δ≤0 and QOL score at 12 weeks <85, n=14) group. As shown in Figure 3, the binding abilities...
of PBMs to LNT in the QOL ‘improved’ group were significantly greater than those in the QOL ‘not-improved’ group, according to a Mann-Whitney U-test (p<0.05).

Discussion

The present study demonstrates the safety and effectiveness of SDL for patients with advanced colorectal cancer. Four adverse events that were or were suspected to have been related to SDL were observed in 4 (5%) out of the 80 patients. All of these symptoms were grade 2 and disappeared or remitted within the study period. Thus, oral SDL treatment, like intravenous LNT treatment, appears to be safe for cancer patients. Regarding the onset of adverse events associated with chemotherapy, 12 adverse events were observed in only 9 (14%) out of 64 patients who received chemotherapy. Among the CPT-11-based regimens, neutropenia (grade 1) was observed in only one patient (4%) and no diarrhea (0%) was observed in the 27 patients. Neutropenia (incidence of all grades, about 70%; grades 3/4, about 30%) and diarrhea (incidence of all grades, about 60%; grades 3/4, about 20%) are usually the main severe adverse events associated with CPT-11-based regimens (23, 24). Among the 5-FU-based regimens, neutropenia and diarrhea were observed in 1 (3%) and 2 (5%) of the 37 patients, respectively. The respective incidences of neutropenia and diarrhea are reportedly 67% (grades 3/4, 31%) and 60% of

of PBMs to LNT in the QOL ‘improved’ group were significantly greater than those in the QOL ‘not-improved’ group, according to a Mann-Whitney U-test (p<0.05).

Discussion

The present study demonstrates the safety and effectiveness of SDL for patients with advanced colorectal cancer. Four adverse events that were or were suspected to have been related to SDL were observed in 4 (5%) out of the 80 patients. All of these symptoms were grade 2 and disappeared or remitted within the study period. Thus, oral SDL treatment, like intravenous LNT treatment, appears to be safe for cancer patients. Regarding the onset of adverse events associated with chemotherapy, 12 adverse events were observed in only 9 (14%) out of 64 patients who received chemotherapy. Among the CPT-11-based regimens, neutropenia (grade 1) was observed in only one patient (4%) and no diarrhea (0%) was observed in the 27 patients. Neutropenia (incidence of all grades, about 70%; grades 3/4, about 30%) and diarrhea (incidence of all grades, about 60%; grades 3/4, about 20%) are usually the main severe adverse events associated with CPT-11-based regimens (23, 24). Among the 5-FU-based regimens, neutropenia and diarrhea were observed in 1 (3%) and 2 (5%) of the 37 patients, respectively. The respective incidences of neutropenia and diarrhea are reportedly 67% (grades 3/4, 31%) and 60% of

of PBMs to LNT in the QOL ‘improved’ group were significantly greater than those in the QOL ‘not-improved’ group, according to a Mann-Whitney U-test (p<0.05).

Discussion

The present study demonstrates the safety and effectiveness of SDL for patients with advanced colorectal cancer. Four adverse events that were or were suspected to have been related to SDL were observed in 4 (5%) out of the 80 patients. All of these symptoms were grade 2 and disappeared or remitted within the study period. Thus, oral SDL treatment, like intravenous LNT treatment, appears to be safe for cancer patients. Regarding the onset of adverse events associated with chemotherapy, 12 adverse events were observed in only 9 (14%) out of 64 patients who received chemotherapy. Among the CPT-11-based regimens, neutropenia (grade 1) was observed in only one patient (4%) and no diarrhea (0%) was observed in the 27 patients. Neutropenia (incidence of all grades, about 70%; grades 3/4, about 30%) and diarrhea (incidence of all grades, about 60%; grades 3/4, about 20%) are usually the main severe adverse events associated with CPT-11-based regimens (23, 24). Among the 5-FU-based regimens, neutropenia and diarrhea were observed in 1 (3%) and 2 (5%) of the 37 patients, respectively. The respective incidences of neutropenia and diarrhea are reportedly 67% (grades 3/4, 31%) and 60% of

of PBMs to LNT in the QOL ‘improved’ group were significantly greater than those in the QOL ‘not-improved’ group, according to a Mann-Whitney U-test (p<0.05).

Discussion

The present study demonstrates the safety and effectiveness of SDL for patients with advanced colorectal cancer. Four adverse events that were or were suspected to have been related to SDL were observed in 4 (5%) out of the 80 patients. All of these symptoms were grade 2 and disappeared or remitted within the study period. Thus, oral SDL treatment, like intravenous LNT treatment, appears to be safe for cancer patients. Regarding the onset of adverse events associated with chemotherapy, 12 adverse events were observed in only 9 (14%) out of 64 patients who received chemotherapy. Among the CPT-11-based regimens, neutropenia (grade 1) was observed in only one patient (4%) and no diarrhea (0%) was observed in the 27 patients. Neutropenia (incidence of all grades, about 70%; grades 3/4, about 30%) and diarrhea (incidence of all grades, about 60%; grades 3/4, about 20%) are usually the main severe adverse events associated with CPT-11-based regimens (23, 24). Among the 5-FU-based regimens, neutropenia and diarrhea were observed in 1 (3%) and 2 (5%) of the 37 patients, respectively. The respective incidences of neutropenia and diarrhea are reportedly 67% (grades 3/4, 31%) and 60%
(grades 3/4, 11%) for IV 5-FU/LV and 11% (grades 3/4, 3%) and 54% (grades 3/4, 18%) for oral UFT/LV (25). According to another report, the incidences of neutropenia and diarrhea for oral UFT/LV were 34% (grades 3/4, 0%) and 39% (grades 3/4, 9%), respectively (26). In addition, in the present study, the incidence of adverse effects (thrombocytopenia/leukopenia) for regimens including S-1 was only 4% (1 out of 24 patients). The incidences of thrombocytopenia and leukopenia associated with S-1 in stage II and III gastric cancer patients (n=517) were reportedly 26% (grades 3/4, 0.2%) and 59% (grades 3/4, 1%), respectively (27), while the incidence of leukopenia was 38% (grades 3/4, 2%) in advanced gastric cancer patients (n=150) (28). Several reports have revealed that anticancer drugs such as CPT-11, paclitaxel, CDDP and 5-FU act by increasing intracellular reactive oxygen species (ROS), and that N-acetylcysteine or mangafodipir (a superoxide dismutase (SOD) mimic) reduce the hematotoxicity of anticancer agents by reducing intracellular ROS (29-31). LNT increases the intracellular reductive glutathione content as well as the N-acetylcysteine content and scavenges ROS by increasing reductive glutathione (14, 15). Thus, the oral administration of SDL may be useful for the suppression of chemotherapy toxicity.

In the present study, we also evaluated the patients’ QOL scores before and after SDL administration in 48 patients with unresectable colorectal cancer. Usually, the QOL status of patients with advanced cancer tends to gradually decrease. In contrast, among the 48 patients in the present study, no significant difference was seen between the QOL scores for before SDL administration and those for after 12 weeks of SDL administration. Thus, the QOL status tended to remain constant for the 12 weeks of SDL administration. In particular, the QOL scores (Activity, Physical, Psychological, Social aspects and Overall score) obtained after 12 weeks of SDL administration were significantly better than those obtained before SDL administration in the QOL low-score group. The overall QOL scores were improved in 15 (65%) of the 23 patients in this group. Some physical aspects (including appetite condition and body weight loss) were significantly improved.

Figure 2. LNT-binding ability of CD14+ monocytes by FACS Histogram. A, without F-LNT (LNT-negative); B, with F-LNT (B-1, dull-positive; B-2, bright-positive).

Figure 3. LNT-binding abilities in QOL ‘improved’ and ‘not-improved’ groups. Forty-eight patients were divided into 3 categories according to their LNT-binding abilities: ≥5%, high; 1.0-4.9%, moderate; <1.0%, low. The numbers in parentheses represent the number of patients in each category. There was a significant difference in the LNT-binding ability between the QOL ‘improved’ and the ‘not-improved’ groups (p<0.05, Mann-Whitney U-test).
improved after 8 weeks of SDL administration. The increased production of prostaglandin E2 (PGE2) in macrophages is reportedly involved in appetite loss and reduced body weight in cachectic mice inoculated with colon cancer cells (32). A previous study demonstrated that LNT reduces PGE2 and increases IL-2 production in macrophages (33). In addition, an experiment confirmed that the administration of LNT significantly increased daily food intake in rats with stress-induced anorexia (34). Moreover, LNT has been proven to inhibit the production of interleukin-6 (IL-6) in macrophages (35), which is known to cause cachexia (36). These findings may support the present finding that SDL may effectively improve QOL in patients with advanced colorectal cancer.

To estimate more objective parameters, we evaluated the binding ability of CD14+ monocytes to LNT. The binding abilities of PBMs in patients with seasonal allergic symptoms reportedly exhibit individual variations, and the binding abilities of PBMs in patients whose symptoms were improved by SDL treatment were significantly higher than those in patients whose symptoms were not improved (16). In the present study, the binding abilities of the PBMs to LNT also showed individual variations, with a median of 3.6% (ranging from 0.2% to 44.4%) in the 48 patients whose QOL statuses were estimated. No significant difference was seen between the QOL ‘improved’ group (n=22; median, 5.3%; range, 0.8-33.8%) and the ‘high-score maintained’ group (n=12; median, 5.0%; range, 0.2-44.4%). The patients in the ‘high-score maintained’ group are patients who responded to SDL. On the other hand, the rate of LNT-bound PBMs in the QOL ‘improved’ group was significantly higher than that in the QOL ‘not-improved’ group (n=14; median, 2.0%; range, 0.4-47.7%). There were several patients whose PBMs exhibited variable (increased) LNT-binding abilities 1 or 2 months after the initiation of SDL treatment (data not shown). These patients may have converted from LNT low-responders to SDL responders as a result of the SDL treatment and/or chemotherapy. These results suggest that the LNT-binding ability of CD14+ monocytes should be estimated at 1 or 2 months after the initiation of SDL treatment to identify SDL responders. As mentioned above, the mode of action of LNT is mediated by host immune competent cells and LNT is reported to bind to monocytes and macrophages, whose binding abilities to LNT exhibit individual variations (16). Although the functional differences between F-LNT bright-positive monocytes and dull-positive monocytes are still unknown and further investigations are required, the LNT-binding ability of CD14+ monocytes may be a promising predictor for the selection of responders to SDL treatment.

In conclusion, SDL was safe and effective for suppressing the adverse effects of chemotherapy as well as improving QOL. The binding ability of PBM to LNT appears to be a promising predictor of QOL improvement after SDL administration.

Acknowledgements

This study was supported by grants from the Digestive Study Group on Foods and Lifestyle-related Disease, an affiliated organization of the Japanese Society of Geriatric Gastroenterology. We thank Ajinomoto Co., Inc., which provided the test samples containing SDL, and Dr. I. Makino, Dr. T. Bamba, Dr. Y. Arakawa, Dr. Y. Atomi and Dr. T. Matsui, who are permanent organizers of the Digestive Study Group on Foods and Lifestyle-related Disease, for their general advice regarding this study. We are also grateful to Dr. A. Kamiya of the Department of Pharmacy of Yamaguchi University Hospital for his kind advice regarding the preparation of the clinical study protocol.

Conflict of Interest Statement

The authors did not have any assistance writing the present manuscript. T. Suga and Y. Suga are employees of Ajinomoto Co., Inc., which holds patents and technologies for the production of SDL. Dr. Nakazawa is the representative organizer of the Digestive Study Group on Foods and Lifestyle-related Disease. No other potential conflicts of interest relevant to this article are present.

References


14 Murata Y, Shimamura T, Tagami T, Takatsuki F and Hamuro J: The skewing to Th1 induced by lentinan is directed through the distinctive cytokine production by macrophages with elevated intracellular glutathione content. Int Immunopharmacol 2: 673-689, 2002.


