III The clinical studies of BioBran

Application of Modified Arabinoxylan from Rice Bran (BioBran/MGN-3) to the Prevention and Supplementary Treatment of Diseases

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Chemotherapy and radiation therapy are effective in cancer treatment, but, as is well known, they are double-edged swords that also damage the body. Pharmaceutical products that cause fewer adverse reactions and maintain QOL have also been developed and are used in the treatment of cancer. However, the highest priority has been given to curing the cancer, and insufficient care is taken to prevent the deterioration of the body's physiological functions. Although there are many health professionals who place importance on the relationship between the prevention of cancer, lifestyle-related diseases and food functions and put this into practice, there are few doctors interested in the benefits of food, at least in the context of cancer treatment. Having doubts about cancer treatment with anti-cancer drugs alone, the present author conducted the following experiment. In a rat model of sepsis induction produced by treating rats with methotrexate, the effect of water-soluble dietary fibre was examined. It was found that dietary fibre acted to prevent sepsis, and a scavenger-like effect was also suggested, indicating the possibility that portal blood was purified by the dietary fibre. We conducted experiments based on this result, and obtained a result that showed that liver metastasis was inhibited by intake of dietary fibre. In other words, cancer could be controlled by dietary fibre.

We surgeons usually prescribe several days of fasting after surgery for gastrointestinal diseases, and then give an easily absorbed, high-nutrition liquid diet followed by thin rice gruel, whose consistency is gradually increased. In contrast, indigestible food containing dietary fibre has been excluded, for the reason that this type of food is a burden to the gastrointestinal tract. However, this works against attempts to purify

the portal blood, and our experiments show that this approach may promote the liver metastasis of cancer.

Several years later, an American research group gave a presentation on a surprising result from a study, which was delivered at an international academic conference on colorectal medicine held in Sweden. They reported that the intake of food containing dietary fibre immediately after surgery had no adverse effect, but in fact rather accelerated postoperative recovery because the bacterial flora was rapidly restored to its state prior to the operation, supporting our experimental result, which showed the possibility that this could inhibit metastasis. The American group's study result suggests that food ingredients are likely to have a therapeutic influence in the treatment of diseases, especially cancer; it implies that dietary fibre improves the intestinal flora, purifying the portal blood, and resulting in improvements in liver function. I believe that this mechanism can eventually lead to enhanced biological defence and spontaneous recovery from cancer.

In basic studies, BioBran/MGN-3 has been shown to exert an immunomodulatory action and improve biological defence mechanisms. The present author confirmed the ability of BioBran/MGN-3 to scavenge reactive oxygen species, and its action in eliminating superoxide anion radicals and hydroxyl radicals in an *in vitro* test, and reported that it might enhance biological defences. Researchers engaged in basic studies of BioBran/MGN-3, including the author, have great interest in its effect on the clinical prevention and supplementary treatment of diseases. The food ingredient has no direct effect on disease, but contributes to its prevention and improvement, by maintaining and increasing biofunctions. Because of this, it is very difficult to evaluate its efficacy and express the results quantitatively. At present, the only way to do this is by following the current evaluation procedure for the efficacy of pharmaceutical products. Given this, clinical trials for BioBran/MGN-3 were conducted and valuable data was obtained. The author performed a double-blind study to evaluate its effect on the prevention of the common cold syndrome in elderly individuals. We confirmed that BioBran/MGN-3 compensated for the decreased ability to prevent infection due to aging and improved cold symptoms by reducing inflammation.

As there are many restrictions on clinical trials of food ingredients in cancer patients, it is difficult to conduct studies for objective assessment, such as double-blind trials. There is therefore no other choice but to accumulate case studies. The author does not believe that cancer treatment can be evaluated by statistically significant differences alone. From the mechanism of food function, it is natural that the onset of effects will vary greatly between individuals because each one has a different nutritional status. It is meaningful to evaluate effects over the long term through observation of clinical course in the same individual in addition to making comparisons between patients. I hope that the future accumulation of more data will lead to the development of effective applications of BioBran/MGN-3 in man.

Life Prolongation and QOL Improvement Effect of Modified Arabinoxylan from Rice Bran (BioBran/MGN-3) for Progressive Cancer

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Key words: complementary alternative medicines, rice bran arabinoxylan derivative, natural killer activity, apothanasia effect

Abstract

The present study was designed to determine whether the administration of BioBran/MGN-3 could have its apothanasia effect and improve QOL for 205 progressive and partially metastasized cancer patients in late III-IV stages after surgery. BioBran/MGN-3 is a rice bran arabinoxylan derivative known to have immunomodulation activity. The participants in this clinical study were hospitalized patients in our clinic treated with complementary alternative medicines ("Non-Conventional Therapy") and anticancer drugs with lesser side effects. The 205 patients hospitalized for 6 months were placed into two groups, viz, 109 patients (control group) treated with our standard complementary alternative medicines, and 96 patients who were further given BioBran/MGN-3 (BioBran/MGN-3 group) for one year and a half.

All patients were monitored for natural killer (NK) cell activity as an indication for the variation of

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immunoparameters. Simultaneously, the QOL of the patients was also checked. The NK cell activities of the patients after surgery were low on average; however, after administration of BioBran/MGN-3, NK activity increased, as did apothanasia ratio; the higher the patient NK activity the higher the apothanasia ratio was observed to rise. These findings indicate that NK activity can be used as a pathological index in progressive cancers. QOL improvement was also observed with the administration of BioBran/MGN-3.

Introduction

We perform a complementary alternative therapy developed in our clinic on progressive cancer patients who have a metastasis or unresectable lesion after surgery to maintain high QOL and prolong survival time, and have obtained good results. This therapy consists of hospitalization and home treatment. The mean duration of hospitalization is 1 month, during which patients are treated and educated for treatment at home. After discharge, they are based on home care and periodically visit the clinic for examination and treatment. This therapy causes no large damage to patients in principle. The main aim of the therapy is to put cancer cells into a dormant state. Normally, this therapy should be used in postoperative patients without recurrence or metastasis. In the present study, however, the life prolongation effect of BioBran/MGN-3 was confirmed in 205 cancer patients in late III-IV stages, including those who had a metastasis or unresectable lesion left after surgery. The purpose of this study was to determine whether the addition of BioBran/MGN-3 to our complementary alternative therapy prolongs survival time and improves QOL by enhancing the original effects of the therapy.

Methods

1. Patients

Subjects were patients hospitalized in our clinic who were treated with a complementary alternative therapy developed here (**Table 1**) and anticancer drugs that induce less severe adverse reactions. They were 205 progressive-cancer patients in late III-IV stages, who had recurrence, unresectable lesions, or metastasis after surgery. The primary lesions were in the lung (31 patients), liver (18), uterus (7), breast (33), prostate (4), rectum (28), stomach (34), lymph node (11), or others (29).

Table 1 Details of Complementary Alternative Therapy

immuno-enhancement:	CDA-II (enzyme in urine), germanium
	mushroom polysaccharides, specific substance Maruyama (SSM)
	oriental medicines, Lymphocytes
diet therapy:	Gerson's special diet therapy, kale vegetable juice, vitamins
intra-intestinal environmental	
improvement:	probiotics, prebiotics
thermotherapy:	far infrared ray, thermotherapy with loquest leaves
blood catharsis:	SOD, coffee enema
psycho-therapy:	thoroughgoing of positive way of thinking by seminars/lectures

Table2 Patients participated in the clinical study, MGN-3 Group and Control Group

Cancer site	MGN-3 Group	Control Group
Lung	14	17
Liver	10	8
Uterine	7	0
Breast	18	15
Prostate	3	1
Large intestine	9	19
Stomach	15	19
Lymph nod	7	4
Others	13	26
Total	96	109
Sex	Male 55, Female 41	Male 59, Female 50
Average age	56.0	53.5

Table 3 Scoring of QOL checkpoints and levels

pain, malaise and nausea		appetite	
none:	0	no appetite:	0
scarcely:	1	scarcely:	1
fairly strong:	2	fairly:	2
strong:	3	good appetite:	3
very strong:	4	-	

2. Investigational substance

BioBran/MGN-3 is a rice bran arabinoxylan derivative obtained by hydrolyzing hemicellulose of rice bran with many glycosidase, which has an immunomodulatory[2-3], active-oxygen scavenging[4], and blood-sugar controlling effects[5], and reduces adverse reactions to anticancer drugs[6]. The brand name of BioBran/MGN-3 is Lentin Plus 1000, manufactured by Daiwa Pharmaceutical Co., Ltd. (Tokyo).

3. Methods

A total of 205 patients who visited our clinic within about 6 months were randomly divided into 2 groups (control and BioBran/MGN-3 groups). The control group was given a treatment prescribed in our clinic, and the BioBran/MGN-3 group was given BioBran/MGN-3 in addition to this therapy. The breakdown of the patients is shown in **Table 2**. BioBran/MGN-3 at 1 g was given orally 3 times a day after meals. The observation period was 18 months, and the patients visited once a month during the period to determine the activity of natural killer cells (NK activity) as an immune parameter. Patients who stopped visits without notice were excluded as dropouts from the study. Patient QOL was checked by observation and enquiry during the study. Pain, malaise, and vomiting were evaluated using 4 grades, and appetite assessed using 3 grades to compare the scores before and after treatment. **Table 3** shows the details.

Table 4 Relation among total survival rate, NK activity and survival rates in 2 groups

Group	MGN-3 Group	Control Group
Total survival rate	52/96 (54.2%)	19/56 (35.8%)
NK activity category		
Less than 19.9%	17/40 (42.5%)**	2/16 (12.5%)
20%-40%	18/35 (51.4%)*	7/25 (28.0%)
More than 40%	17/21 (81.0%)	10/15 (66.7%)

*significant to the control group **$p < 0.01$ *$p < 0.05$

Table 5 QOL amelioration

QOL	Pain			Malaise			Nausea			Appetite		
	BT	AT	%	BT	AT	%	BT	AT	%	BT	AT	%
Control group	2.9	2.5	-14.0	3.5	2.9	-17.1	2.5	2.9	-14.6	1.6	1.9	+15.6
MGN-3 group	2.2	1.9	-15.9	2.9	2.4	-17.3	2.3	2.0	-13.3	1.7	2.1	+24.2

Note; BT: Before treatment AT: After treatment

%: Amelioration degree = (Scores at initiation less scores at termination) divided by scores at initiation

(-): indicates negative factors (decrease), (+): indicates positive factors (increase).

Results

1. Subjects included in analysis

A total of 152 of 205 patients were eligible for analysis, including 96 in the BioBran/MGN-3 group and 56 in controls. The main reasons for dropping out were that the prescribed treatment became impossible due to increased pain, malaise, or vomiting, and decreased appetite due to cancer progression in some cases, or that other patients were pessimistic and gave up the prescribed treatment. There were no dropouts in the BioBran/MGN-3 group, and all patients were included in the analysis. In the control group, 53 patients, accounting for 49%, dropped out.

2. The number of surviving patients and survival rates at 18 months

The survival rate at 18 months of treatment was 54.2% for the BioBran/MGN-3 group (52 patients) and 35.8% for the control group (19). An investigation showed that no dropout survived. This means that the survival rate for the control group was 17.4% of 109 patients at the start of study.

3. Changes in NK activity

After starting the study, patients had decreased, unchanged, or increased NK activity. In the BioBran/MGN-3 group, NK activity fell in 45.9% of patients, was unchanged in 21.9%, and increased in 32.3%. In the control group, NK activity fell in 51.8%, was unchanged in 9.0%, and increased in 39.3%. There was no difference in patients with increase or decrease in NK activity between both groups, but the rate of patients with unchanged NK activity was higher in the BioBran/MGN-3 group.

4. Relation between NK activity and prolongation of survival

NK activity before completion of the study was classified into categories of ≤20%, 20%-40%, and ≥40% to compare survival rates. The survival rate was higher in patients with higher NK activity in both groups. The results are shown in **Table 4**.

5. QOL

Table 5 shows mean QOL scores and improvements (%) before and after treatment for 96 patients in the BioBran/MGN-3 group and 56 in the control group.

Improvement of QOL was observed in both control and MGN-groups, suggesting that our clinic's complementary alternative therapy is effective in improving QOL for patients with progressive cancer. In particular, the BioBran/MGN-3 group showed a marked increase in appetite.

Conclusion

The life prolonging and QOL improving effects of BioBran/MGN-3 were studied in progressive cancer patients given a clinic-prescribed therapy and those given the same therapy plus BioBran/MGN-3. As a result, clear prolongation of life expectancy and QOL improvement were observed. The mean duration of hospitalization was 1 month. Although the maintenance of patients numbers was not perfect during the study, a total of 205 participated in the study, and data were obtained from 152 of them. This is sufficient for statistical analysis. The patients' NK activity was clearly decreased, and the survival rate tended to be low in patients with decreased NK activity. The proportion of patients with unchanged or increased NK activity was higher in the BioBran/MGN-3 group than in the control group, resulting in a 1.5 times higher survival rate in the former group. There are many reports on the NK activity modulating effect of BioBran/MGN-3, and the results of the present study supported this. With respect to QOL appetite clearly increased in the BioBran/MGN-3 group. While 49% dropped out in the control group, there were no dropouts in the BioBran/MGN-3 group. This was at least in part because of the improvement of the nutritional state due to increased appetite.

The relation between NK activity and immunity against a tumor is controversial, and the role of NK cells is not completely clear. However, it is considered a good indicator of nutritional status in progressive cancer patients, because those with NK activity above a certain level are likely to survive for a longer time. Preventing NK activity from declining and maintaining it at a high level may lead to prolongation of survival.

BioBran/MGN-3, which helps the maintenance and enhancement of patient's self-curative ability, can be a useful tool for complementary alternative therapy.

Finally, we would like to thank Daiwa Pharmaceutical for supplying BioBran/MGN-3 and Mitsubishi Chemical Laboratory (B.C.L.) for cooperation in blood tests.

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NK Immunorestoration of Cancer Patients by BioBran/MGN-3, A Modified Arabinoxylan Rice Bran (Study of 32 Patients Followed for up to 4 Years)

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NK cells have been characterized as non-B cells or non-T cells lacking the characteristics of mature mocrophages which develop from the bone marrow independently of thymic influence[1,2]. NK cells play a crucial role in tumor rejection, immune surveillance, resistance to infections, and immune regulation[3-5]. NK cell destruction of cancer cells involves a sequence of events[6]. First, the NK cell recognizes and binds to the cancer cell. This process requires receptor-to-receptor interaction. Next, the NK cell releases granules which penetrate the cencer cell and ultimately kill it. The NK cell is then free to bind to another cancer cell and repeat the same process.

However, cancer cells know how to fight back in a sort of cell war. We found for the first time in our laboratory that cancer cells can destroy WBCs throught the phenomenon of phagocytosis[7-10]. We have observed three ways in which this is done. The cancer cell can extend two arms around the WBC or it can develop a cup-shaped opening where the WBC is drawn inside. A third way is for the cancer cell to extend a long arm to capture the WBC and finally draw it inside the cancer cell where it is digested. In addition, extensive work by others has shown that cancer cells secrete immune-suppressive substances which inhib-

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it the function of the immune system[11-13].

Many attempts have been made in the last 25 years to strengthen the power of the immune system using different biological response modifiers (BRMs). These are substances originating from bacteria and fungi which possess immunoaugementory properties[4, 14, 15]. In addition, some kinds of cytokines serve as BRMs such as interferons, interleukin-2 and interleukin-12[16, 17]. There are two problems associated with these BRMs: 1st) toxicity and 2nd) the development of hyporesponsiveness in which a single administration of the BRM can significantly enhance NK cell activity, but that repeated administration of the same BRM results in depression of NK cell activity[18-20]. It is interesting to note that BioBran/MGN-3 has advantages over other BRMs. It is nontoxic and has not shown hyporesponsiveness in the four years that the patients have been followed. This work was undertaken in order to investigate the augmentory effect of a new BRM known as BioBran/MGN-3 on NK cell function and T and B cell proliferation in 32 patients. Tumor-associated antigens were reported for selected patients.

Patients, Materials and Methods

1. Patients

The present study was carried out on 32 cancer patients. Patients had different types of malignancies: prostate[10], breast[12], multiple myeloma[5], and leukemia. The majority of the patients first went through a debulking done using conventional therapies such as surgery, radiation, or chemotherapy.

2. Materials

BioBran/MGN-3 is an arabinoxylan extracted from rice bran that is treated enzymatically with an extract from shiitake mushrooms. It is polysaccharide that contains (-1,4 xylopyronase hemicellulose. MGN-3 is commercially known as Biobran (Daiwa Pharm., Co., Ltd., Tokyo, Japan).

3. Methods

(1) Treatment Protocol.

Patients were given BioBran/MGN-3 (3 g/day) daily by mouth.

(2) Tumor-Associated Antigens (TAA).

TAA for each type of malignancy was measured prior to BioBran/MGN-3 treatment and one month post-treatment.

(3) Tumor Cell Line.

K562, a human erythroleukemic cell line, was used as the target. Tumor cells were cultured in complete medium (CM) that consisted of RPMI-1640 supplemented with 10% fetal calf serum and 1% antibiotic (100 U penicillin and 100 g/m*l* streptomycin).

(4) Preparation of Peripheral Blood Lymphocytes (PBL).

PBLs were prepared from fresh heparinized peripheral venous blood by Ficoll-Hypaque density gradient contrifugation. Cells were washed two times with Hanks balanced salt solution (HBSS) and resuspended to 10×10^6 cells/m*l* in CM.

(5) ^{51}Cr-Release Assay for Measuring NK Activity.

NK activity was measured by a standard 4 hr ^{51}Cr-release assay. Briefly, 1×10^4 ^{51}Cr-labelled tumor target cells in 0.1 m*l* CM were added to different wells of a 96-well microtiter plate. Effector cells were then

pipetted into quadruplicate wells to give E: T ratios of 12: 1, 25: 1, 50: 1, and 100: 1. After a 4 hr incubation at 37℃, the plates were centrifuged (1,400 rpm for 5 min) and 0.1 m*l* of supernatant from each well was collected and counted in a gamma counter (Beckmann G50, Beckmann Instruments).

The percentages of isotopes released were calculated by the following formula:

$$\% \text{ Lysis} = \frac{\text{Exp. Rel.} - \text{Sp. Rel}}{\text{Total Rel.} - \text{Sp. Rel}} \times 100$$

(6) Spontaneous release (SP) from target cells was no more than 8-10% of total release.

Total release was measured by adding 0.1 m*l* Triton X-100 (Sigma Chemical Co.) to designated wells. Lytic units (LU) were calculated from effector titration curves with one LU defined as the number of effector cells required to achieve 20% lysis for K562.

(7) NK Granularity.

Percall frationated PBL were adjusted to 2.5×10^6 cells/m*l* and centrifuged on slides at 1,000 rotation/minute for 5 minutes using a cytospin cytocentrifuge (Shandon Southern Institute, Sewickley, PA). Slides were air dried, fixed in 100% MeOH, stained with 5% Giemsa solution for 10 minutes. Stained preparations were examined for the granularity NK cells [21].

(8) *In Vivo* T and B Lymphocyte Proliferation.

We investigated the *in vivo* effects of BioBran/MGN-3 on T and B cell proliferation using 3H-thymidine uptake. MNCs were prepared from peripheral blood of five cancer patients before and at one month after treatment with BioBran/MGN-3. Cells were incubated at 2×10^5 cells/m*l* in CM. Cells were treated with 10 g/m*l* of phytohemagglutinin (PHA), concanavalin A (Con A), or pokeweed mitogen (PWM) for three days. One Ci of 3H-thymidine (New England Nuclear) was added to the cell cultures for the last 18 hrs. DNA was harvested and 3H-thymidine uptake was determined by scintillation counter. All experiments were done in triplicate and data expressed as counts per minute (cpm).

(9) Statistical Analysis.

Student T test was used to examine the significance of difference between NK activities and T and B cell response to mitogens before and after treatment with BioBran/MGN-3.

Results

1. NK cell activity

Fig.1 demonstrates the baseline values of cytotoxic responses of NK cells in 32 cancer patients. Patients demonstrated overall significant low level in NK function. Depression in NK activity was observed in patients with different types of malignancies as follows: prostate, 11.1 LUs; breast, 11.4 LUs; MM, 7.3 LUs ; and leukemia, 4.3 LUs. Studies performed on peripheral blood lymphocytes from 12 participants one to two weeks after the primary studies revealed no statistically significant differences in NK cell activity in comparison with the initial results. Treatment with BioBran/MGN-3 resulted in significant increase in NK activity up to tenfold. BioBran/MGN-3 augmentory effect was detected in all types of malignancies: prostate, 41.9 LUs; breast, 33 LUs; MM, 31.9 LUs; and leukemia, 51.4 LUs. Individuals varied in response to augmentory effect of BioBran/MGN-3.

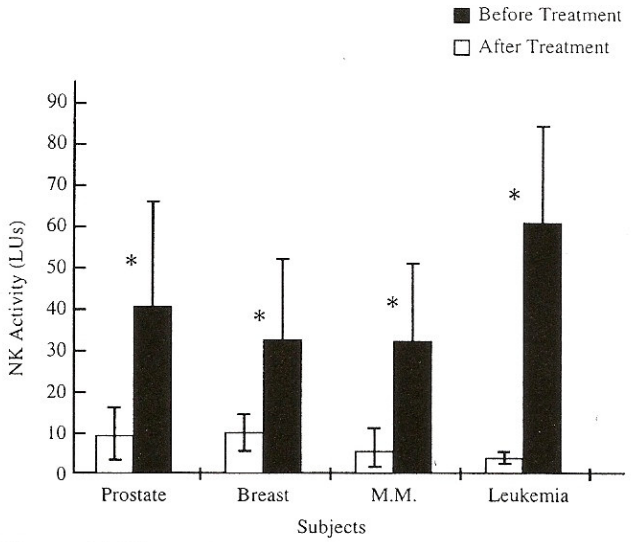

Fig.1 Effects of MGN-3 on NK cell activity of 32 patients at one to two weeks after treatment.

Malignancies were: prostate (10), breast (12), multiple myeloma-MM (5), and leukemia (5).

LUs at 20% *P<0.001.

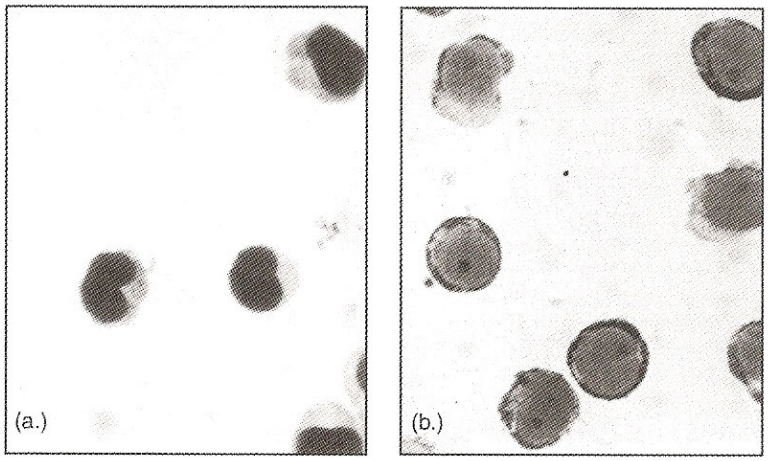

Fig. 2

(a) : Cytocentrifuge preparation of PBL-NK cells isolated from cancer patient before treatment with MGN-3. (Giema, X740).

Notice high nuclear cytoplasmic ratio and absence of granules.

(b) : Cytocentrifuge preparation of PBL-NK cells of the same patient at one weel post-treatment with MGN-3. Cells demonstrated high granular content.

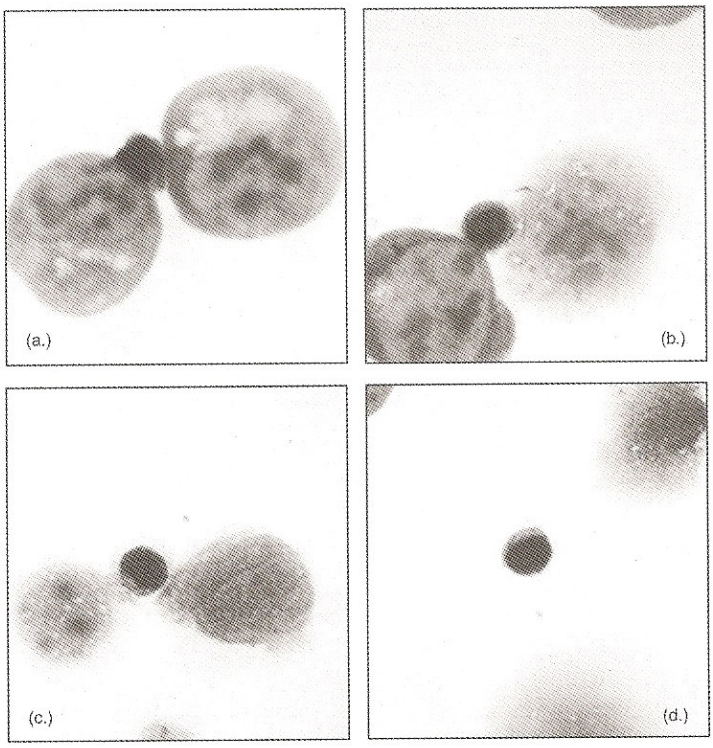

Fig. 3 Cytocentrifuge preparation of two K562 tumor cell destruction by one NK cell. NK cells were activated by MGN-3.

(a) First step in the process represented by binding of NK cell to tumor cells. (Giema, X740).

(b) Preparation showing one tumor cell is dead. (Giema, X740).

(c) Preparation showing both tumor cells are dead while NK cell in between is still alive. (Giema, X740).

(d) Cytocentrifuge preparation showing NK cell detach itself from the dead tumor cells. (Giema, X740).

2. NK Granularity

Cytospin cytocentrifuge preparation of PBL-NK cells before treatment showed low or absent granularity (**Fig. 2-a**). On the other hand, treatment with BioBran/MGN-3 resulted in significant increase in the granular content at one week post-treatment (**Fig. 2-b**). The BioBran/MGN-3-activated NK cells demonstrated an increase in the binding capacity and killing of cancer cells (**Fig. 3**).

3. *In Vivo* T and B Lymphocyte Proliferation

Fig.4 shows that treatment with BioBran/MGN-3 significantly increased T cell proliferation as indicated by their response to PHA and Con A mitogens. B cell proliferation also increased post-treatment with BioBran/MGN-3 as indicated by their response to PWN, a B cell mitogen, as compared to baseline value.

4. TAA and NK Activity in a Selection of Patients

Patients were monitored for tumor-associated antigens: prostate, PSA; and multiple myeloma, BJP or

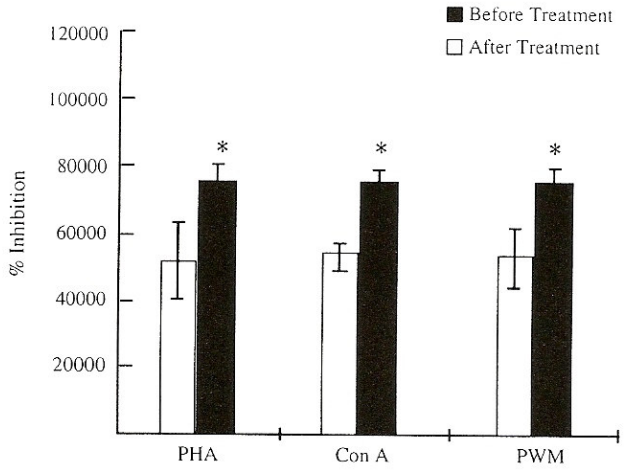

Fig. 4 ***In vivo*** **action of MGN-3 on T and B cell mitogen response at one month after treatment.**

MNC were cultured for three days in the presence of PHA, Con A and PWM. Data represent mean (S.D. of five individuals. *P<0.001).

IGg; while breast cancer was monitored by CEA and CT Scan one to two times per year. A selection of patients having different types of malignancies were analyzed.

A 39-year-old patient, Mr. K., diagnosed with acute myelogenous leukemia (AML), was treated with chemotherapy which brought the WBCs count to 5.6, the normal range being between 4.5 and 10.5. He was off chemo and began taking BioBran/MGN-3 in January of 1995. His WBC count has been within the normal range from that time. The patient's baseline NK activity was 7.9 LUs and increased to 113 LUs within one week after treatment with BioBran/MGN-3. His NK activity level has remained high for about four years now.

Mr. Y., a 52-year-old Japanese store manager, was also diagnosed with AML. He did not follow conventional therapy. His WBC was 18,700 per milliliter on March 31, 1998. He began taking BioBran/MGN-3 and on April 30th his WBC dropped to 11,000. His condition has been kept quite stable since that time.

In 1994, Mr. R. came to us suffering from prostate cancer. Hormonal therapy had brought his PSA level to 0.1 but it was known that the marker would increase again with time. The patient was given BioBran /MGN-3 and his PSA level has remained within the normal level for the last four years.

Ms. M. had a recurrence of breast cancer in April of 1995 and was treated with surgery followed by chemotherapy. She started BioBran/MGN-3 after completion of her chemotherapy and since then all CAT scans have been negative. There has been no evidence of recurrence seen in CAT scans or biopsies. The patient's baseline NK cell activity was 16.4 LUs, which increased twofold one week post-treatment with BioBran/MGN-3. Her activity increased further to 128 LUs and has remained at a high level over the years.

Discussion

BioBran/MGN-3 is considered to be a potent BRM as manifested by inducing increased activity of NK cells in animals and humans. Mice injected IP with BioBran/MGN-3 showed a several-fold increase in NK cell activity at two days post-treatment. Other studies where BioBran/MGN-3 was mixed with food and fed to rats also demonstrated increased NK cell activity in a dose-dependent manner. Studies were also carried out on healthy subjects who received BioBran/MGN-3 orally. A 2.3-fold increase in NK activity was seen at one week post-treatment with BioBran/MGN-3 at 30 and 45 mg/kg/d while lower doses of 15 mg/kg/d took one month to increase NK activity by twofold[22].

We thought it would be of particular interest to investigate the augmentory effect of BioBran/MGN-3 on NK activity in cancer patients. Patients went through chemotherapy or radiation therapy as debulking was necessary. However, NK activity becomes depressed as a result of these therapies. Given a need for natural immunity in tumor control, we felt it may be clinically important to enhance NK activity in order to destroy the remaining cells that escape from chemo and radiation. It is possible to enhance NK cell activity with the usage of different BRMs. However, toxicity and hyporesponsiveness associated with many BRMs limit their usage. BioBran/MGN-3 is a safe product and patients did not develop hyporesponsiveness during the four years of the study. NK cells are sensitive indicators of activation by BRMs. Their monitoring has been used to document alterations in the activity of sirculationg immune cells during therapy with these agents. Enhancement of NK activity by BioBran/MGN-3 was detected as early as one to two weeks post-treatment and it was manitained at a high level with continuation of BioBran/MGN-3 treatment.

The therapy of debulking followed by BioBran/MGN-3 immunotherapy had a practical application in the 32 cancer patients. Parallel to the increase in NK activity, patients demonstrated a gradual decrease in the level of TAAs with signs of recurrence for the four years of the study.

The mechanism(s) by which BioBran/MGN-3 increases NK cell activity has been examined. Based on our studies, it appears that two mechanisms are involved in the activation of NK cells by BioBran/MGN-3. First, by the increase in NK cell granularity and second, by the elevation of cytokine production. Regarding granularity, NK cells in our patients have low granularity or granules might be absent altogether. It is interesting to note that BioBran/MGN-3 treatment significantly increases the granular content of NK cells (**Fig. 2**). The granules are not only situated in the cytoplasmic portion but also between the nuclear and cellular membranes. Exocytosis of NK granules and secretion of pore-forming molecules (perforins) stored as cytoplasmic granules may represent one of the most important mechanisms to kill cancer cells by the NK cell system[23-25]. The important role of granules in NK cells' destruction of their tumor targets has been indicated by the observation that isolated and purified granules are lytic for a variety of tumor cell types[24]. Therefore, we believe that the increased level of granularity of NK cells is an important factor in the enhancement of these effector cells by BioBran/MGN-3.

With respect to cytokines, several cytokines have been shown to affect NK cell proliferation or cytolytic activity. Of these, the interferons (IFN) and IL-2 have been the most extensively studied[16, 17, 26, 27]. Suppression in NK activity in cancer patients was related to defective lymphokine production. It appears that augmentation of NK cell cytotoxic function by BioBran/MGN-3 is parallel to a significant increase in the levels of different cytokines. The heavy granulation of LGL may indicate secretory function. It is not

known whether production of various lymphokines is a multipotential property of a single subset of LGL. It is more likely that different subsets of LGL are responsible for different lymphkines. *In vitro* studies showed that PBLs treated with BioBran/MGN-3 have significantly increased production of TNF- (and IFN-)[28]. In addition, patients with different types of malignancies showed an increase in levels of IL-2, IL-12, TNF- (and IFN-) post-treatment with BioBran/MGN-3 (data not shown), suggesting that the apparent enhancement in NK cytotoxicity by BioBran/MGN-3 could be cytokine mediated.

Our work has shown primarily the dramatic effect of BioBran/MGN-3 on NK cells; however, there is evidence obtained from healthy control subjects that other immune cells, T cells and B cells, have shown increased function post-treatment[29]. In this study, we have found that patients also demonstrated elevation of T and B cell function as evidenced by their proliferation response to different mitogens. This suggests that BioBran/MGN-3 causes overall immune stimulation.

The preliminary results of the present studies are encouraging enough to warrant continued investigation in multiple clinical trials.

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III-1-3

Effect of Long-term Administration of Immunomodulatory Food on Cancer Patients Completing Conventional Treatments

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Key words : Complementary medicine, Rice bran arabinoxylan derivative, Immunomodulatory food, Safety

Summary

A study was conducted to investigate the effects of long-term administration of the immunomodulatory food modified arabinoxylan from rice bran (BioBran/MGN-3), on 16 cancer patients, mainly in stage IV with various conventional lesions, who had just undergone conventional cancer treatments, such as surgery, chemotherapy and radiotherapy. The main clinical observations were the safety and effect of BioBran/MGN-3 on the nutritional state of the patients, who were exhausted due to treatment. During the administration period, no decrease in body weight and leukocyte count or significant changes in leukogram were observed. Rather, the leukocyte count increased. In addition, most patients showed an increase in NK cell activity and a remarkable decrease in tumor markers.

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Introduction

In our clinic, complementary medicine is used in cancer patients who have completed surgery, chemotherapy, and irradiation therapy in order to improve QOL, prevent recurrence, and enhance life prolongation. We call the medicine "Ryo-yo." "Ryo" means treatment given in the clinic to enhance healing and immunity, and "yo" means daily care by the patients themselves to increase their self-healing capacity. For daily care, patients are trained in breathing, diet, and physical and mental health[1]. The diet should be based on modern dietetics or grains and vegetables to enhance prophylactic effect. Functional foods are also used as part of the dietary therapy, but patients make their own decision about ingestion. Many functional foods are used to prevent decreased immunity and to reduce adverse reactions during cancer treatment. All our patients take up to 5 kinds of functional foods. Most contain ingredients equal or similar to those in foods taken every day. However, the form is as concentrates and capsules, granules, or tablets of partially purified ingredients in most cases. Thus, there is a possibility of ingesting larger quantities of some ingredients than those contained in foods. As it is reported that excessive ingestion of β carotene promotes lung cancer[2], sufficient attention should be paid to safety. In the present study, the effect of long-term administration of BioBran/MGN-3, most frequently used by our patients, was evaluated in 16 cancer patients with nutritional problems who had just completed conventional treatments, focusing particularly on the effect on leukocytes.

Table 1 Backgrounds of subjects

Initials	Age	Sex	Primary lesion	Study period
K.O.	56	Male	Stomach	January to July 2001
I.R.	64	Male	Large intestine	March to September 2001
M.T.	59	Male	Large intestine	March to September 2001
K.K.	44	Female	Breast	February to August 2001
T.H.	58	Female	Rectum	May to November 2001
F.A.	46	Female	Breast	July 2001 to January 2002
T.S.	60	Female	Stomach	August 2001 to February 2002
K.H.	47	Female	Breast	December 2001 to June 2002
E.I.	44	Male	Biliary tract at hepatic portal	February to August 2002
H.Y.	59	Female	Large intestine	February to August 2002
H.M.	77	Female	Ovary	December 2001 to June 2002
M.N.	72	Female	Thyroid gland	January to July 2002
Y.I.	44	Male	Lung	October 2001 to April 2002
Y.H.	84	Male	Rectum	January to July 2002
N.A.	39	Female	Uterine cervix	March to September 2002
K.M.	53	Male	Rectum	April to October 2002

Table 2 Changes in body weight (kg)

Initials	Before study	After study	Difference
K.O.	70.0	71.0	+1.0
I.R.	67.0	69.0	+2.0
M.T.	61.0	60.0	-1.0
K.K.	48.0	49.0	+1.0
T.H.	53.0	53.0	0
F.A.	49.0	51.0	+2.0
T.S.	38.0	38.0	0
K.H.	52.5	53.0	+0.5
E.I.	47.0	46.5	-0.5
H.Y.	50.0	51.0	+1.0
H.M.	44.0	44.0	0
M.N.	46.5	47.0	+0.5
Y.I.	64.0	65.0	+1.0
Y.H.	59.0	60.0	+1.0
N.A.	45.0	46.5	+1.5
K.M.	68.0	68.0	0

Table 3 Changes in leukocyte count and subsets

Initials	Leukocyte count (/mm^3)			Neutrophil (%)			Lymphocyte (%)		
	Before administration	After administration	Difference	Before administration	After administration	Difference (%)	Before administration	After administration	Difference (%)
K.O.	5500	6500	+1000	65.7	76.2	+10.5	24.9	19.5	-3.4
I.R.	6100	4400	-1700	69.8	62.8	-7.0	24.1	27.6	+3.5
M.T.	3500	4100	+600	56.4	59.5	+3.1	27.2	31.2	+4.0
K.K.	3400	3600	+200	60.8	64.9	+4.1	22.7	21.3	-1.4
T.H.	5700	5400	+300	51.9	53.0	+1.1	42.0	42.5	+0.5
F.A.	2500	3000	+500	57.0	52.1	-4.9	24.5	42.5	+18.0
T.S.	3800	4200	+400	40.0	55.3	+15.3	56.0	35.9	-20.1
K.H.	4800	4400	-400	80.0	71.7	-8.3	11.0	20.6	+9.6
E.I.	2800	3400	+600	57.9	67.0	-9.1	25.6	23.8	-1.8
H.Y.	4200	5400	+1200	50.5	61.9	-11.4	33.7	27.2	-6.5
H.M.	3000	3500	+500	54.6	63.8	+9.2	30.3	29.9	-0.4
M.N.	7300	6000	-1300	68.9	62.2	-6.7	24.6	28.7	+4.1
Y.I.	3700	5600	+1900	71.7	82.0	+10.3	19.7	11.5	-8.2
Y.H.	5600	5800	+200	64.0	64.2	+0.2	25.2	23.5	+1.7
N.A.	5200	4300	-900	80.0	71.1	-8.9	13.5	14.2	+0.7
K.M.	5300	5900	+600	44.8	48.8	+4.0	35.7	23.6	-12.1

Table 4 Changes in leukocyte count and subsets from the normal ranges

	Leukocyte count		Neutrophil		Lymphocyte	
	Before administration	After administration	Before administration	After administration	Before administration	After administration
L	7	4	-	-	11	13
N	9	12	8	5	4	3
H	-	-	8	11	1	-

Table 5 Categorization of changes in leukocyte count and subsets

	Leukocyte count	Neutrophil	Lymphocyte
Increase	9	5	2
No change	4	5	10
Decrease	3	6	4

Table 6 Changes in NK activity

Patient's initials	Before administration	At 6 months of administration
K.O.	13.3	31.2
I.R.	17.0	47.5
M.T.	37.2	50.3
K.K.	4.1	45.3
T.H.	9.5	34.8
F.A.	9.3	39.5
T.S.	25.6	38.6
K.H.	15.9	63.6
E.I.	16.2	39.4
H.Y.	9.6	6.1
H.M.	22.5	31.4
M.N.	31.4	20.3
Y.I.	32.4	32.0
Y.H.	30.3	30.2
N.A.	20.3	10.7
K.M.	8.2	26.2

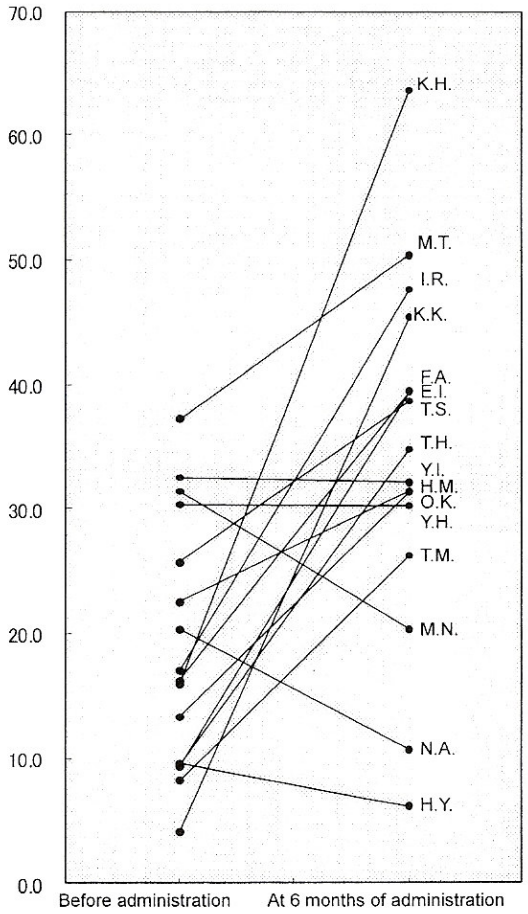

Fig. 1 Changes in NK activity

Methods

1. Patients and study period

The subjects were 16 cancer patients who met the criteria (1) to (3) below, and the study period was 6 months.

Table 1 shows the age, primary lesion, and study dates for each patient.

1) Cancer patients just after completion of surgery, irradiation therapy, and/or chemotherapy

2) Patients visiting this clinic for observation of outcome and care to improve QOL and prevent recurrence

3) Patients who consented to ingest BioBran/MGN-3 at 3 g/day.

2. Study items

The study items were body height and weight, leukocyte count and subsets (neutrophils, lymphocytes,

monocytes, eosinophils, basophils, and band cells), NK cell activity, tumor markers, adverse reactions (abdominal pain, vomiting, and an enlarged feeling in the abdomen), and interruptions of administration and the reasons for interruption.

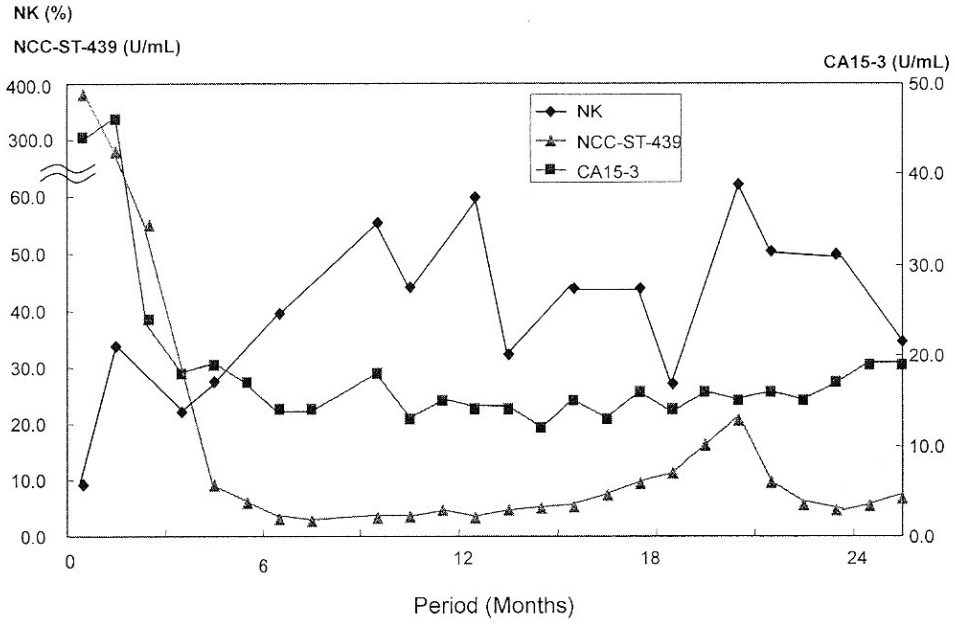

Fig. 2 Breast Cancer (Stage IV) F.A. (46) F.

Height was measured at the start of the study. Body weight and leukocyte count and subsets were monitored 3 times at the start of, during, and at the end of the study. NK activity and tumor markers were determined every month. Adverse reactions and interruptions of ingestion were checked throughout the study period.

3. Modified arabinoxylan from rice bran (BioBran/MGN-3)

The study material BioBran/MGN-3 is produced by partially hydrolyzing rice bran extract with enzymes. There are many reports on the physiological actions of MGN-3, the generic name of BioBran, including immunomodulation[3-4], active-oxygen scavenging[5], blood sugar control[6] and reduction of adverse reactions to anticancer drugs[7].

Results

All 16 subjects completed the administration of BioBran/MGN-3 continuously during the study period.

1. Changes in body weight

Body weight increased in 10 patients, decreased in 2, and was unchanged in 4. The range of change was

within 4% for both increase and decrease. BioBran/MGN-3 had almost no effect on body weight. **Table 2** shows these changes.

2. Changes in leukocytes

Changes in leukocyte counts and subsets were studied. **Table 3** shows leukocyte counts and results for neutrophils and lymphocytes. The normal range is 4000-9000/mm^3 for leukocytes count, 40%-60% for neutrophils fraction, and 30%-45% for lymphocytes. Individual measurements before and after administration were divided into categories H (higher than the normal ranges), N (within the normal ranges), and L (lower than the normal ranges) (**Table 4**).

The changes in measurements were classified into the categories of increase (changes above 10% for leukocyte counts and 5% each for neutrophil and lymphocyte fractions), no change (changes within ±10% and ±5% each, respectively), and decrease (changes under -10% and -5% each, respectively) (**Table 5**).

The leukocyte count was generally low in the subjects of this study because they had just completed conventional treatments: it was below the normal range in 7 of 16 patients (44%).

After 6 months of BioBran/MGN-3 administration, leukocyte count increased in 9 of 16 patients, of whom 3 had a normal value. The fraction of neutrophils increased slightly, but no constant trend was observed. The lymphocyte fraction was low, and there was almost no change before and after administration. In one patient each, however, the value changed from a low level to the normal range and from a high level to the normal range. Overall, changes towards a healthy condition were observed, and no adverse changes were noted in the leukocyte profile for 6 months.

3. NK activity and tumor markers

The NK activity at the start of the study was ≤ 30% in 11 patients, 30%-50% in 3, and ≥ 50% in 2, and the proportion of patients with normal NK activity was 19%. After administration of BioBran/MGN-3, NK cell activity tended to increase, and was normal in 11 patients (69%). Tumor markers decreased in 10 (63%) after administration of BioBran/MGN-3.

Fig. 1 and **Table 6** show changes in NK activity.

4. Adverse reactions

No adverse reactions to BioBran/MGN-3 were observed or reported by any of the subjects.

5. Cases with marked improvement in nutritional state

1) Patient: F.A., female, 46 years, recurrent breast cancer (stage IV)

The patient received a diagnosis of breast cancer in July 1998 and underwent surgery and hormonal treatment. After 2 years 6 months, she had metastases in the left iliac bone, lumbar vertebrae, and uterine body. A hysterectomy was performed and Taxol and Paraplatin administered for bone metastases. However, no improvement was observed, and metastases to the thoracic vertebrae and ribs occurred. She visited our clinic in July 2001, when the tumor markers CA15-3 and NCC-ST-439 were at the high concentrations of 44 U/mL and 369 ng/mL, respectively, and NK activity was at a low level of 9.3%. She had malaise, severe bone pain, and low QOL (PS2). She received our therapy while continuing administration of Paraplatin. BioBran/MGN-3 was taken at 3 g/day. NK cell activity increased to 33.7% at 1 month, and the levels of two tumor markers decreased rapidly at 2 months. By 7 months, pain due to bone metastases disappeared and

malaise was reduced. Now, after 34 months (April 2004), she lives a normal life with QOL maintained (PS0) (**Figure 2**).

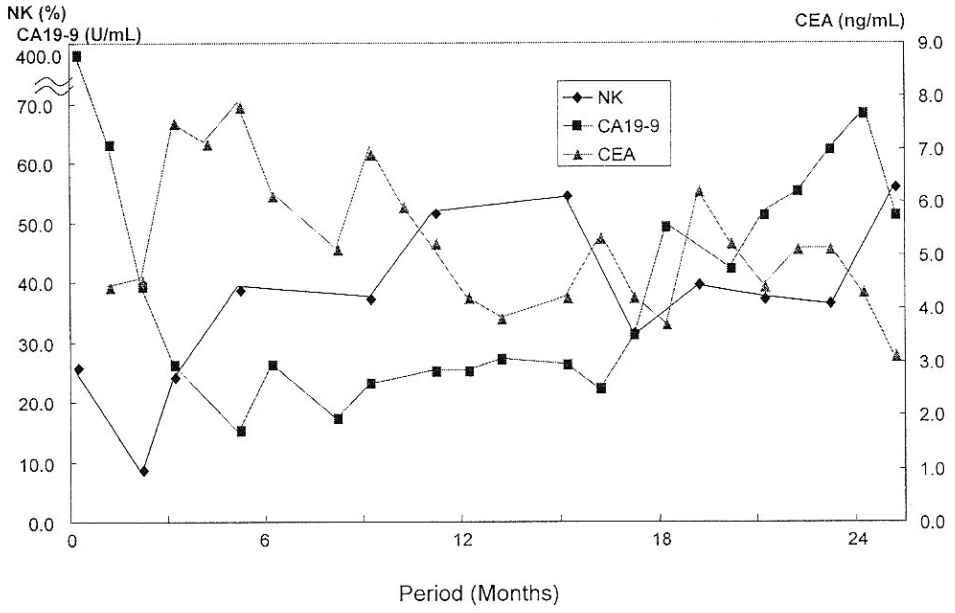

Fig. 3 Stomach Cancer (Stage IV) T.S. (60) F.

2) Patient: T.S., female, 60 years, stomach cancer (stage IV)

This patient underwent surgery for scirrhous carcinoma of the stomach, but curative resection was impossible because of cancerous peritonitis. She visited our clinic in August 2001 and complained of abdominal pain, an enlarged feeling in the abdomen, anemia, and anorexia (PS1). She was given the oral anticancer drug TS-1 and our hospital's therapy. BioBran/MGN-3 was taken at 3 g/day. The level of CA19-9 was 390 (U/mL) at the first visit and reduced to within the normal range by 3 months. The level of CEA increased, but began to fall at 6 months. Subjective symptoms gradually improved. Now, at 33 months (April 2004), her nutritional state is good, and she lives a normal life (PS0) (**Fig. 3**).

Discussion

During administration of BioBran/MGN-3, the patients' nutritional status was good, with no exacerbation in subjective and objective symptoms. Overall improvement was observed. The leukocyte count was low in many cases at the start of the study, but increased in almost all patients at the end of the study, and some achieved a normal value. Our clinic's complementary medicine maintains good physical conditions in high frequency after conventional cancer treatment. The conditions of patients in the present study were especially good, with no large difference in nutritional state between patients and healthy individuals. NK activity tended to increase: the number of patients with normal NK activity improved from 3 before the

study to 11 after the study. These results supported data reported from other institutions[8]. These phenomena were not clearly observed in patients who were not given BioBran/MGN-3.

Long-term administration of BioBran/MGN-3 had no adverse effects, such as compromised immunity, in cancer patients after conventional treatment, suggesting that BioBran/MGN-3 is useful as a dietary therapy that assists the improvement of the nutritional state.

Conclusion

Long-term administration of BioBran/MGN-3 caused no subjective or objective adverse effects in cancer patients with decreased immunity. Improvement, rather than adverse changes, was observed in leukocyte counts and subsets. The NK cell activity was decreased at the baseline, but normalized after administration.

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A Case Where an Immunomodulatory Food was Effective in Conservative Therapy for Progressive Terminal Pancreatic Cancer

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Key words: pancreatic cancer, rice bran Arabinoxylan derivative, complementary medicine, ACM π water

Summary

A patient with terminal pancreatic cancer accompanied by distant metastasis who was unfit for radical surgical treatment was treated with BioBran/MGN-3, which is reported to have a biological defense action, and π water, which can enhance the blood circulation and transportation of nutrients and drugs (Vehicle action), in addition to low toxicity chemotherapeutic agents in order to maintain biological functions and QOL. As a result, satisfactory therapeutic effects were obtained, such as improvements in biological functions and spontaneous power of recovery.

Introduction

The author has a great deal of experience in endoscopic examination of the stomach and large intestine

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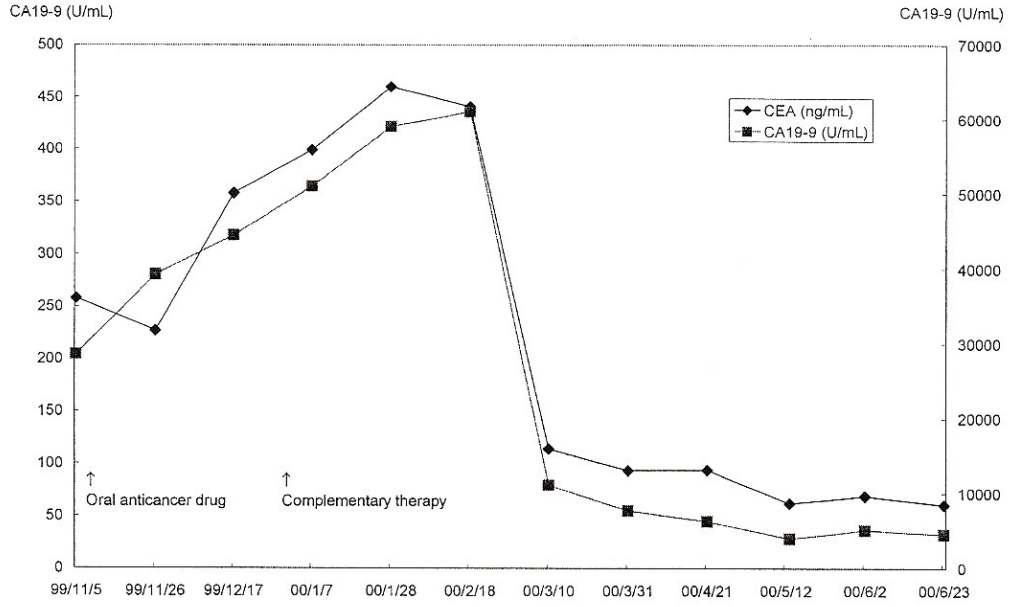
and has achieved results in the early detection and prevention of stomach and large-intestinal cancer. When a diagnosis of early-stage cancer within the mucous membrane is made as a result of examination, resection is performed by endoscopy. When laparotomy is required, radical operation is performed in hospitals in cooperation with our clinic. In inoperable cases, however, chemotherapy is used for life prolongation, and conservative therapy is given at the same time for improvement of QOL. The author uses oral anticancer drugs that cause fewer adverse reactions in inoperable patients unless aggressive ones are desired, because adverse reactions of chemotherapy generally affect the patient's nutritional state in cases of terminal cancer, and conservative therapy is not effective in a poor nutritional state. In addition, functional foods with biophylactic activity are combined to reduce adverse reactions and enhance the effect of chemotherapy.



Graph 1 Changes in tumor markers in patient with pancreatic cancer

Anticancer drugs that cause fewer adverse reactions were combined with functional foods in a patient with progressive terminal pancreatic cancer who was judged inoperable, and a marked therapeutic effect was obtained.

1. Case presentation

A 64-year-old man with a history of type II diabetes mellitus had subjective symptoms of epigastric pain and anorexia and visited our clinic in November 4, 1999. Endoscopy revealed unclearly defined enlargement of the mucosal fold with easily haemorrhagic erosion on the posterior wall of the upper gastric corpus (**Figure 2a**). It was diagnosed as Group V, well-differentiated adenocarcinoma by biopsy. Another lesion of early cancer (stage II a + II c) was noted on the anterior wall of the angular lesser curvature stomach at the same time (**Figure 3a**, arrow). CT examination showed that the lesion on the upper gastric

corpus was pancreatic cancer. The tumor penetrated the gastric wall from behind the stomach and reached the upper posterior wall. This was a very rare case, where stomach biopsy detected pancreatic cancer. Many liver metastases were also noted with ascites fluid retention. For tumor markers, CEA was 258.0 ng/mL, and CA19-9 was 28,600 U/mL on November 5, 1999. Radical surgery was judged impossible, and chemotherapy was tried. As the patient wished to have treatment on an outpatient basis, oral anticancer drugs that cause fewer adverse reactions (Furtulon 1,200 mg/time and Endoxan 200 mg/time) were administered.

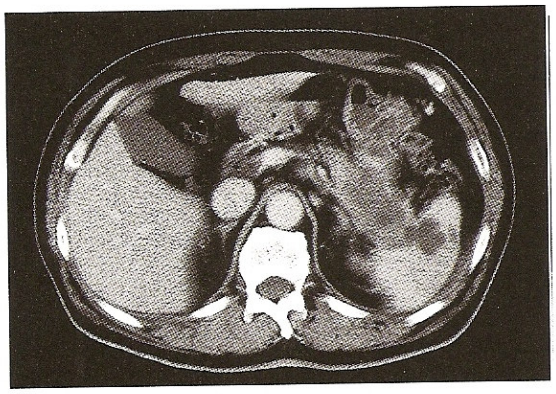


Figure 1a

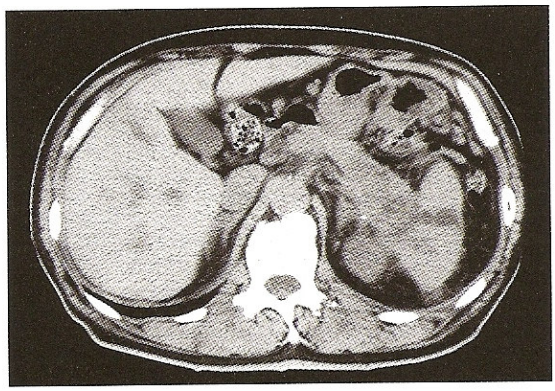


Figure 1b

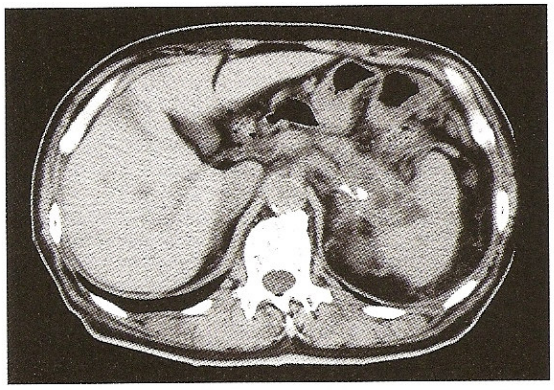


Figure 1c

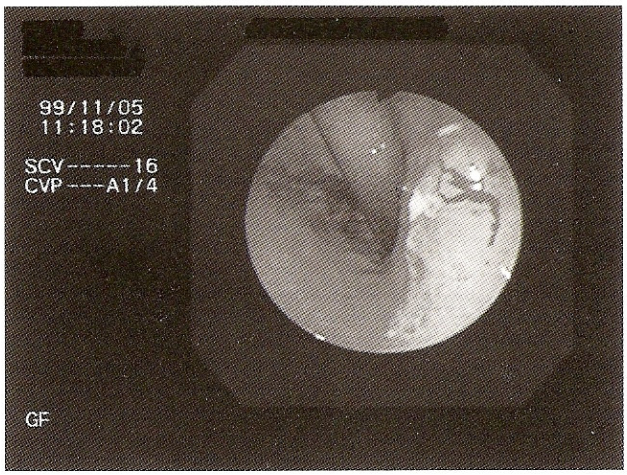


Figure 2a

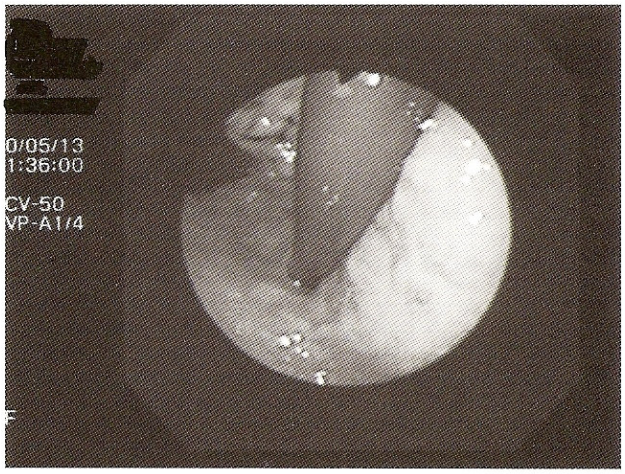


Figure 2b

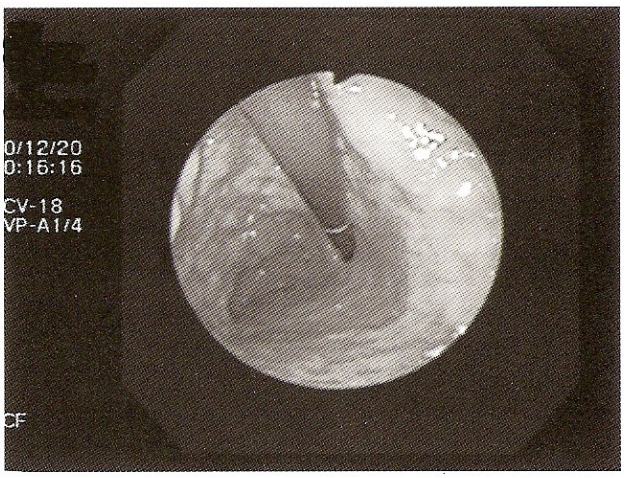


Figure 2c

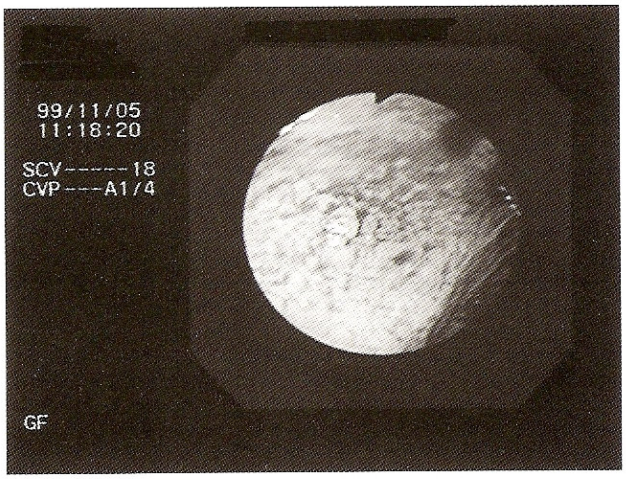


Figure 3a

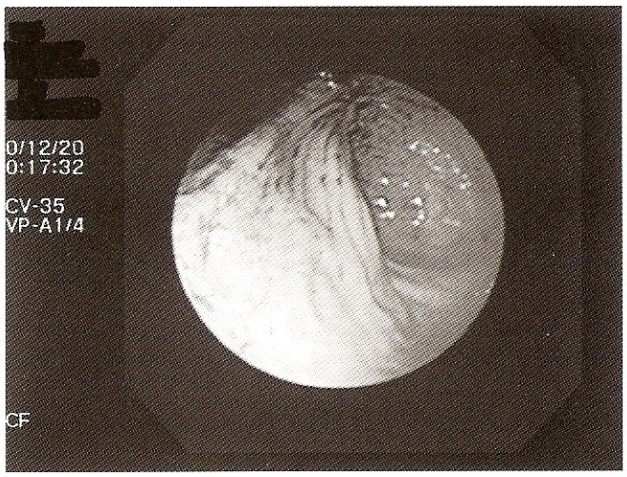


Figure 3b

The conservative therapy and observation were continued for a period, but the tumor markers rose rapidly (CEA: 460.0 ng/mL; CA19-9: 54,000 U/mL), and anorexia and pain increased. At the patient's request, complementary therapy was commenced with BioBran/MGN-3 (brand name Lentin Plus 1000, Daiwa Pharmaceutical Co., Ltd.)[1] and ACM π water (brand name MRN-100A, ACM Co., Ltd.)[2] from January 7, 2000, about 2 months later.

2. Clinical course and results

Graph 1 shows changes in tumor markers, **Figures 1a, b,** and **c** CT scan images, and **Figures 2a, b,** and **c** endoscopic findings over time.

At the time of the first revisit on January 7, 2000, the patient started Lentin Plus, containing 1 g of BioBran/MGN-3 in each parcel (6 parcels/day), and ACM π water (MRN-100A) (300 mL/day) for nonspecific immunomodulation and biophylactic improvement.

When the therapy started on January 7, 2000, the leukocyte count was 7,800/mm^3, lymphocytes were

1,856/mm^3, and granulocytes were 3,723/mm^3. The leukocyte count was maintained; but the level of lymphocytes was low, inflammatory monocytes increased to 608/mm^3, and the CD4/CD8 ratio was low, showing decreased cellular immunity.

From January 28, 2000 (about 1 month after treatment initiation), the increase in tumor markers stopped (CEA 441 ng/mL; CA19-9 61,000 U/mL), ascites retention and anorexia improved, body weight began to increase at the same time, and nutritional state clearly improved. On CT images, however, the diameter of the pancreatic tumor was about 5 cm, and liver metastatic lesions were unchanged. On March 31, 2000 (3 months after treatment initiation), the tumor markers rapidly decreased (CEA 93.6 ng/mL, CA19-9 6,300 U/mL, leukocyte count 6,120/mm^3, lymphocyte count 1,678/mm^3, granulocyte count 3,654/mm^3, and monocyte count 586/mm^3).

CT images showed marked reductions of the pancreatic cancer and liver metastases (**Figure 1b**). **Figures 1c** and **2b** show CT images and endoscopic findings obtained on May 13, 2000 (5 months after treatment initiation). The diameter of the pancreatic cancer was almost unmeasurable, and the liver metastases reduced in the same way. Endoscopic examination showed a marked reduction in mucosal prominence. On December 20, 2000, there was almost no abnormality, and only a scar-like ulcer remained (**Figure 2c**). Early cancer on the anterior wall of the angular lesser curvature stomach completely disappeared (**Figure 3b**, arrow). A biopsy revealed no malignant tumor cells.

The remaining life expectancy of this patient with progressive terminal cancer was judged to be about 3 months at first visit. However, ingestion of the rice bran arabinoxylan derivative and ACM π water, in addition to Furtulon, produced a dramatic therapeutic effect. He died of haematemesis in another hospital on April 13, 2001. The cause was not judged to be cancer, because there was no increase in tumor markers just before death. For QOL, he was able to live a normal life for about 17 months.

3. Discussion

Patients with pancreatic cancer are tending to increase in number in Japan. The death rate for pancreatic cancer is high, and the prognosis is very poor[3]. Pancreatic cancer at a very early stage is considered curable by operation. In spite of advanced diagnostic imaging technology, however, most cases detected are advanced and not resectable[4]. This case was also diagnosed as terminal pancreatic cancer with liver metastases and judged not resectable. The oral anticancer drugs Furtulon and Endoxan, combined with functional foods, caused dramatic tumor reduction and QOL improvement. Improvement in biological functions may have induced natural cure of the terminal cancer. The patient had the decreased sugar metabolism peculiar to pancreatic cancer, but the combination therapy allowed easy control of blood sugar, and a good nutritional state was maintained. It has been reported that the rice bran arabinoxylan derivative improved sugar metabolism in models of types I and II diabetes mellitus. This effect may partly contribute to an improvement in nutritional state in the patient. The author combines anticancer drugs that cause fewer adverse reactions, such as UFT, 5FU, and Endoxan, with BioBran/MGN-3 and ACM π water in patients with progressive terminal stomach, large-intestinal or breast cancer in whom radical treatment might have been impossible, and has noted life prolongation and improvement of QOL in many cases. This therapy is one treatment option that prolongs the lives of patients with terminal cancer while preserving physical strength and maintaining QOL.

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III-1-5

A Case of a Patient with Umbilical Metastasis of Recurrental Cancer (Sister Mary Joseph's Nodule, SMJN) Who has Survived for a Long Time under Immunomodulatory Supplement Therapy

Tomonori KAWAI
Shinkurashiki icho komon geka

Key words: Colorectal cancer, Immunotherapy, Rice bran arabinoxylan derivative

Summary

A 64-year-old female patient with umbilical metastasis of recurrent colorectal cancer (SMJN) was treated by complementary medicine using the rice bran arabinoxylan derivative[1-2], a food component of BRM activity, in addition to chemotherapy, in order to maintain QOL and prolong survival. Although the umbilical metastasis tends to grow, the patient is in a good nutritional condition and has survived for more than two years from diagnosis. SMJN is a distant metastasis, and even with the first occurrence, radical treatment may not be possible in most cases. This case suggests that the maintenance of the QOL and physiological function may lead to prolongation of life even in patients with terminal cancer with extremely poor prognosis. This case also presents the benefits of supplementary therapy using functional foods.

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III-1-5 A Case of a Patient with Umbilical Metastasis of Recurrental Cancer (Sister Mary Joseph's Nodule, SMJN)

Introduction

Umbilical metastasis of malignant tumors in visceral organs is known as Sister Mary Joseph's Nodule (SMJN). This is named after Sister Mary Joseph, a nurse working in an operating room, who noticed that gastric-cancer patients with umbilical metastasis had a poor prognosis[3]. The primary lesion is in the

Table 1 Cases of umbilical metastasis of colorectal cancer

No.		Age	Sex	Description and size of tumor	Treatment and others	Primary lesion	Complications	Type of cancer cells	Survival
1	Tameaki Matsubara[5] 1972	62	Female	2 × 1.5 cm Uneven, elastic hard, reddish brown	New patient	Sigmoid colon	Intestinal obstruction 2 weeks after examination	adenocarcinoma	
2	Shojiro Moriyasu[6] 1975	56	Female		New patient	Cecum		cystic papillary adenocarcinoma	
3	Ninako Nakayama[7] 1976	58	Female	Soybean sized, red, hard tumor	Numerous metastatic foci in the greater omentum and small intestine Confirmatory operation	Cecum		adenocarcinoma	
4	Keiko Oka[8] 1981	58	Male	5 × 4 cm Red and cartilage-hard	New patient 5FU (250 ng/day) and Picibanil (0.1 KE/day) Removal of a tumor on the abdominal wall skin	Ascending colon	Liver metastasis	adenocarcinoma	Died after 11 months
5	Yoshinori Mori[9] 1980	45	Female	0.9 × 1.1 cm Milk-white to light yellow Hard, like a plate of a few centimeters around the navel	First patient Krestin (3 g/day)	Ileocecal junction	Liver metastasis, pulmonary edema	adenocarcinoma papillotublare	Died of hepatic coma pneumonia after 10 months
6	Yuichiro Koizumi[10] 1985	56	Female	Hemorrhagic umbilical tumor (the size of index finger's nail)	New patient Removal of the primary lesion	Sigmoid colon		adenocarcinoma	
7	Kazuo Sasaki[11] 1987	64	Male	Fingernail sized, elastic hard, hemisphere, red node	New patient Confirmatory operation	Transverse colon		adenocarcinoma (Moderately differentiated)	Died of pneumonia and renal failure after 2 weeks
8	Masashi Kanazawa[12] 1992	23	Female	Red/renal-enlarged nodular mass	Old patient 5FU (3500 mg/W) Umbilical resection	Transverse colon	Ovarian and peritoneal metastases	signetring cell + mucinous carcinoma	7 months
9	Yoshifumi Kajimoto[13] 1993	67	Female		New patient Tumor removal	Transverse colon	Intestinal obstruction	adenocarcinoma (Moderately differentiated)	3 months
10	Junichi Mizushima et al.[14] 1995	62	Female	3 × 1.4 cm Bone-like hard, subcutaneous tumor	New patient Tegafur 600 mg/day	Sigmoid colon	Metastatic liver tumor	adenocarcinoma (Moderately differentiated)	2 months
11	Eiji Meguro et al.[15] 1998	66	Male	3 × 3 cm	New patient Umbilical tumor removal	Sigmoid colon	Peritoneal metastasis Cachexia	adenocarcinoma	20 days
12	Tomonori Kawai This patient	64	Female	3 × 3.7 cm Bone-like hard, reddish-brown tumor	Old patient Immunotherapy, 5FU, Leucovorin, and Topotecin	Ascending colon	Peritoneal metastasis	adenocarcinoma (Well differentiated)	Surviving for 2 years or more, alive

stomach, pancreas, ovary, or large intestine, but the metastatic route is controversial. Our search showed that there are 11 reports on SMJN originating from colorectal cancer (**Table 1**). We report here the case of a patient with SMJN from the ascending colon who has survived for a long time under chemotherapy and supplement therapy with the immunomodulatory functional food, modified arabinoxylan from rice bran (BioBran/MGN-3).

1. Case presentation

Patient: Female aged 64
Main complaint: Umbilical tumor
Family history: (–)
Medical history: She was diagnosed as having colorectal cancer in April 2000, and underwent a resection of the ascending colon.
Effusion appeared in January 2001, and an umbilical lump was found.
She received a diagnosis of recurrent cancer, peritoneal dissemination, and umbilical metastasis, and was told that surgery was impossible and that her remaining life expectancy was a few months.
She visited our hospital for immunotherapy on January 29, 2002.
Present disease: A 3.0 × 3.9 cm elliptical pink tumor of tooth-like hardness was felt in the navel region, which formed a 7.0 × 5.0 cm unclearly defined mass of the same hardness deep in the abdominal cavity (**Figure 1**).

Test results at admission

WBC: 5900/mm^3
RBC: 4,650,000/mm^3
Platelet: 22.7/mm^3
CEA: 6.1 ng/ml
NK cell activity: 41% (normal 18-40)
AST/ALT: 17/14
Abdominal CT (**Figure 2**)
Pathological tissue (**Figure 3**)
The peripheral blood and immunity were normal, but the tumor marker CEA was at a high level of 6.1 ng/ml.

III-1-5 A Case of a Patient with Umbilical Metastasis of Recurrental Cancer (Sister Mary Joseph's Nodule, SMJN)

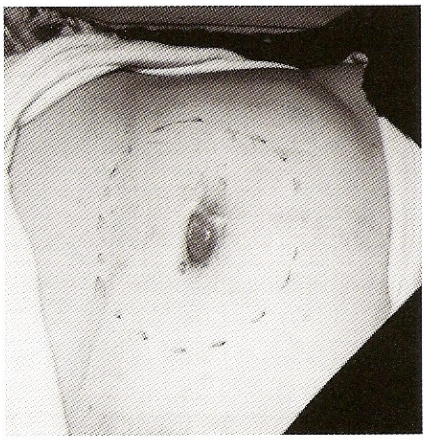


Figure 1

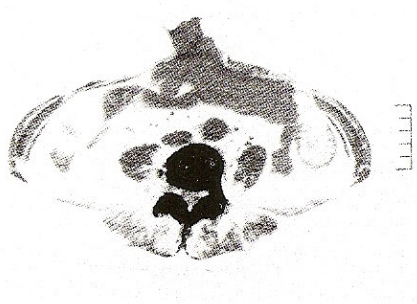


Figure 2

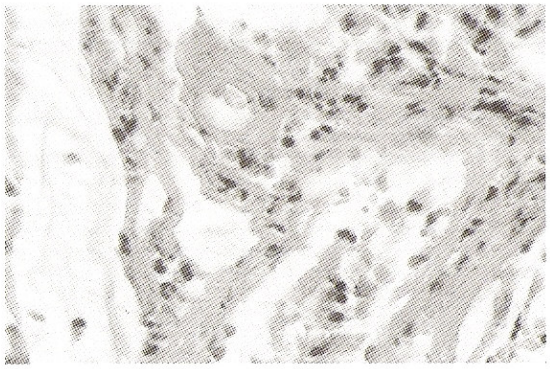


Figure 3

2. Treatment and clinical course

Table 2 shows the content of treatment and clinical course.

The upper section shows changes over time in CEA, WBC count, RBC count, and NK cell activity. The middle section shows the content of treatment, and the lower indicates the tumor size.

1) January 2002

She rejected administration of anticancer drugs for fear of adverse reactions, and thus immunotherapy only was prescribed. BioBran/MGN-3 was taken at 3.0 g/day. The CEA was 6.5 ng/ml and the NK cell activity was 41%. The size of the umbilical tumor was 3.0 × 3.9 cm, and the intraperitoneal mass was 7.0 × 5.0 cm (**Figure 2**).

She had a good appetite and defecation/flatus once a day, being in good condition. She walked into the consulting room.

2) February 9, 2002

NK cell activity increased to 54% after 1 month of BioBran/MGN-3 ingestion.

The CEA decreased slightly to 6.1 ng/ml. She reported that "The umbilical tumor is unchanged, but the intraperitoneal mass is a little reduced."

3) March 15, 2002

The CEA further decreased to 5.6 ng/ml, and the abdominal tumor was unchanged. BioBran/MGN-3 was given for 6 months.

4) July 2002

NK cell activity increased to 55%, but the CEA also increased to 12.6 ng/ml.

The umbilical/intraperitoneal mass slightly increased to 5.0 × 6.0/10.0 × 12.0 cm. She had a good appetite and defecation/flatus.

5) December 2002

The umbilical/intraperitoneal mass was 5.0 × 6.0/10.0 × 12.0 cm. The CEA increased to 24 ng/ml. She had a good appetite and defecation/flatus, but reported, "My stomach is heavy." Her walking condition was good.

6) April 2003

There was no major change from early 2003, but CEA gradually increased to 46.8 ng/ml.

A left inguinal lymph node metastasis was noted. A metastasis of 1.2 × 1.2 cm occurred on the left skin and was removed. The umbilical/intraperitoneal tumor increased to 7.0 × 8.0/29.0 × 24.0 cm, and the dose of BioBran/MGN-3 was increased to 6 g/day. The umbilical tumor discharged a large volume of effusion and she reported, "It is a big problem to keep changing the gauze." However, she traveled occasionally, together with her daughter.

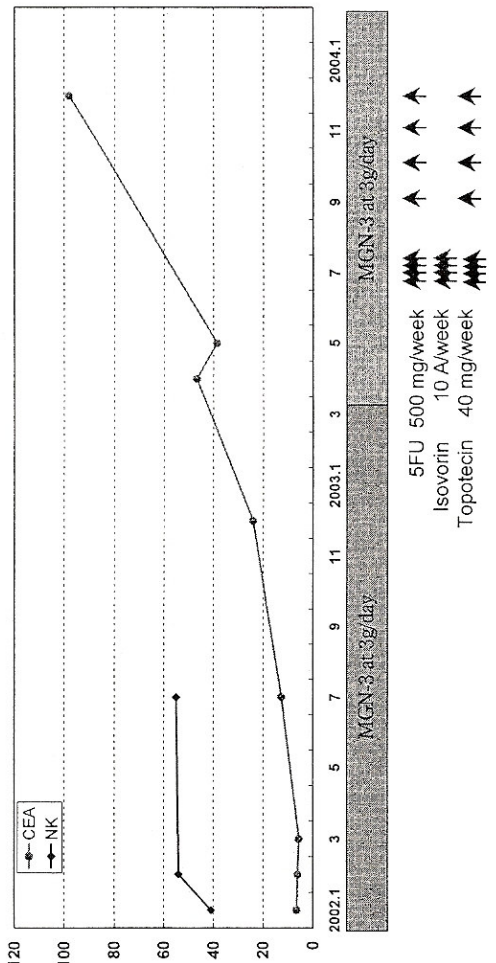
7) May 2003

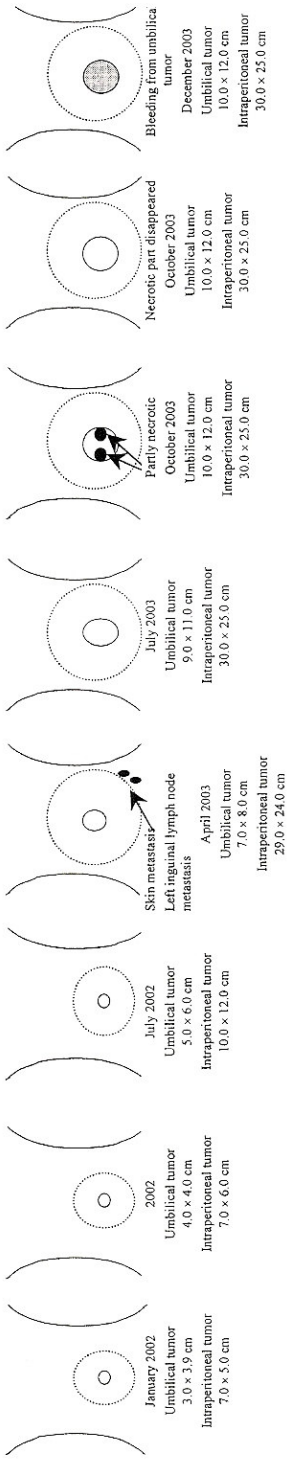
CEA decreased to 38.6 ng/ml. General condition was good. No large change. BioBran/MGN-3 was taken for a total of 1 year and 5 months.

8) July 2003

Since the umbilical/intraperitoneal tumor increased to 9.0 × 11.0/30.0 × 25.0 cm, chemotherapy was performed after obtaining her consent. She reported, "It is hard to walk, because my stomach is heavy." The weight of the mass was estimated from the size to be about 3 kg. She had a good appetite and defecation/flatus.

Table 2 Therapy Details and their Progressions





5FU 500 mg, Isovorin 250 mg (10A) + Topotecin 40 mg were administered once a week, but there were no adverse reactions such as nausea, vomiting, diarrhea, or anorexia.

9) October 2003

The tumor partly became necrotic along the blood vessels after the start of chemotherapy, but the necrotic part disappeared and the tumor began to increase again 4 days after the completion of chemotherapy.

10) December 2003

CEA increased to 98 ng/ml. There was bleeding from the tumor. In spite of astriction with Oxytzel, Spongel, and Tacho Comb, bleeding recurred. However, anemia was not clear, and the RBC count was 3,000,000/mm^3. At her request, chemotherapy was withdrawn and immunotherapy alone given. The WBC count increased to 16900/mm^3, which is possibly because of inflammation due to cancer. The chemotherapy caused no myelosuppression. The appetite slightly decreased, but no nausea or vomiting occurred. She weakened and walked with the help of a stick. The enlarged abdomen from the tumor hindered her from walking.

11) February 2004

The appetite decreased and she ate only half the meals. She weakened further and often lay down. She reported, "When I walk, I always lean back because of my heavy stomach." She walked along the wall to the lavatory. Malaise was mild. She was still alive on February 17.

Discussion

SMJN originates from primary cancer in the stomach, ovary, pancreas, or other areas, and the mean remaining life expectancy is said to be 9.8 months. To the author's knowledge, between 1970 and now, there have been 12 cases of SMJN from colorectal cancer, including this patient (**Table 1**). Survival times are from 2 weeks to 11 months, with an average of 4.9 months, which is shorter than those for other SMJN. Our patient has survived for 2 years and 2 months since detection, and there have been no other similar cases. In comparison of survival time and the tumor size at detection, a patient with a tumor of 0.9 cm survived for 10 months (Case 5), while those with a tumor of 3 cm lived for only 2-3 months (Cases 10 and 11). However, a patient with a large tumor of 4 cm did survive for 11 months (Case 4).

Although Cases 10 and 11 had the same size tumor (3.0 × 3.7 cm) and survived for only 2-3 months, our patient has survived for 2 years or more. Based on these findings, tumor size is not related to prognosis.

The possible reasons for prolonged survival in this case are as follows:

1) As shown in **Table 2**, the patient treatment was based on immunotherapy, which did not impair the immunity determined as NK cell activity.
2) Chemotherapy was added, but no myelosuppression occurred.
3) BioBran/MGN-3 for immunotherapy prevented decrease in physical strength and appetite. The patient also reported, "When I take it, I feel better."
4) Although the abdominal tumor gradually grew in size, the intraperitoneal mass was not so large, which avoided organ compression and complications such as intestinal obstruction due to direct invasion of the large and small intestines, and ascites due to peritoneal metastasis. She also had no liver, lung, brain, or bone metastasis, which occur through hematogenous dissemination.

5) BioBran/MGN-3 produced no adverse reactions.

These may have protected the patient's QOL and prolonged her survival. From now on, she will be followed up using immunotherapy alone.

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III-1-6

The Clinical Significance of Modified Arabinoxylan from Rice Bran (BioBran/MGN-3) in Immunotherapy for Cancer

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Chairman of the Association for Bio-Defense Therapy

Key words: immunotherapy, rice bran arabinoxylan derivative, BRP (Bio-Reproducing Protein)

Abstract

The clinical treatments for cancer include (1) surgery, (2) radiotherapy and (3) chemotherapy with anticancer drugs. For surgery, even where the procedure used is highly sophisticated, cancer cells may be transported to other organs via the vascular or lymphatic systems. Radiotherapy destroys cancer tissues but may also damage the surrounding functioning tissues. Anticancer drugs may destroy cancer cells as well as normally functioning cells of other organs.

Consequently, these drawbacks of the three types of treatments must be recognized when addressing cancer patients. This is where immunotherapy counts. The author has been working with immunotherapy for 25 years, and on this occasion chose combination therapy with BioBran/MGN-3, and BRP (Bio-Reproducing Protein) administered intravenously.

This paper is a translation of an article in *Clinical Pharmacology and Therapy*, 14(3): 289~294, 2004

Case 1. K. M. 67-year-old, M. Liver cancer with intestinal metastasis
Case 2. M. O. 65-year-old, M. Liver cancer
Case 3. F. M. 71-year-old, F. Liver cancer
Case 4. H. H. 76-year-old, F. Lung cancer
Case 5. T. O. 58-year-old, M. Colorectal cancer with liver metastasis

In the above five cases, blood samples were taken once a month to measure tumor markers and immunopotency, and the results were compared with changes in clinical condition. Improvements were noted in all cases.

Table 1 Case 1 (K.M. 67 years, male, liver cancer with intestinal metastasis)

Test item / Time of treatment	LDH (IU/l 37°C)	PIVKA-II (mAU/ml)	α-FP (ng/ml)	CEA (ng/ml)	TK activity (U/l)
Before treatment	392	5,467	132.3	4.4	17.8
1 year of treatment	377	10,234	4,360.0	4.6	46.0
2 years of treatment	314	195	12.2	4.4	9.0
3 years of treatment	349	299	81.4	5.6	6.3
4 years of treatment	366	763	188.0	13.6	6.9
5 years of treatment	177	4,688	5,854.0	52.8	8.5
6 years of treatment	194	4,990	3,262.0	29.7	13.0
Normal value	115-245	< 40	≤ 20.0	≤ 5.0	≤ 5

Methods

The immunotherapy used was oral ingestion of BioBran/MGN-3[1)] combined with intravenous infusion of BRP (Bio-reproducing Protein)[2)]. The therapeutic effect was determined by measuring the levels of tumor markers and immunocompetence.

BioBran/MGN-3 was taken orally at 3.0 g/day (1.0 g × 3), and BRP was infused intravenously once every 4 weeks.

Results

Results in 5 cases are reported.

1. Case 1 (K.M., 67 years, male, liver cancer with intestinal metastasis)

The patient had liver cancer diagnosed and underwent treatment for about 1 year at a training-designated hospital with over 500 beds, but did not obtain good results. The attending physician reported to his family, "He has about 1 month of life remaining, and there are no more treatment options. You should take him home." He had no choice other than discharge and visited our hospital.

For 6 years after the first visit on December 4, 1997, he worked hard and maintained a normal daily life. The test results are shown in **Table 1**. The general condition (LDH), tumor markers (PIVKA-II, α-FP, and CEA), and immunocompetence (TK activity) rapidly improved after 2 years of treatment, he has had no

symptoms until now, and the fecal color has changed from white to normal.

PIVKA-II and α-FP have tended to increase after 5 years of treatment, but LDH maintained a good level, suggesting the effect of the long-term immunotherapy on the cancer.

Now that he has entered his 7th year of treatment, he keeps on working (as a company president) almost normally and makes monthly business trips while receiving treatment on an outpatient basis.

BioBran/MGN-3 was administered for a total of 157 days.

2. Case 2 (M.O., 65 years, male, liver cancer)

The patient received treatment at 2 medical institutions, including a university hospital, but obtained no good result before he visited our hospital for the first time on April 22, 2002. Laboratory tests at first visit showed impaired liver functions (GOT and GPT), increased marker for liver cancer (α-FP), and poor immunocompetence (TK activity). At 6 months of treatment, liver-cancer marker and the immunocompetence improved, but GOT and GPT showed further increases. Both GOT and GPT decreased at 1 year of treatment, and the levels were maintained at 1 year 11 months of treatment (see **Table 2**). During this period, jaundice disappeared, appetite improved, no pain occurred, and there were no special findings. The increases in GOT and GPT compared with the pretreatment values at 6 months suggested serious liver dysfunction due to the cancer.

BioBran/MGN-3 was administered for a total of 72 days.

Table 2 Case 2 (M.O. 65 years, male, liver cancer)

Test item / Time of treatment	GOT (IU/l 37°C)	GPT (IU/l 37°C)	α-FP (ng/ml)	TK activity (U/l)
Before treatment	84	120	57.8	6.5
6 months of treatment	126	185	26.8	5.3
1 year of treatment	48	64	10.1	6.2
1 year 6 months of treatment	58	75	8.8	5.3
1 year 11 months of treatment	66	91	15.2	5.4
Normal value	10-40	5-45	≤ 20.0	≤ 5

Table 3 Case 3 (F.M. 71 years, female, liver cancer)

Test item / Time of treatment	CA19-9 (U/ml)	PIVKA-II (mAU/ml)	α-FP (ng/ml)	TK activity (U/l)
Before treatment	72	55	1,865	4.9
3 months of treatment	104	197	1,699	4.4
6 months of treatment	48	34	2,781	3.6
1 year of treatment	29	14	1,839	2.5
Normal value	≤ 37	< 40	≤ 20.0	≤ 5

Table 4 Case 4 (H.H. 76 years, female, lung cancer)

Test item / Time of treatment	TPA (U/l)	TK activity (U/l)
Before treatment	128	11.0
1 month of treatment	93	8.6
2 months of treatment	117	11.0
3 months of treatment	132	9.1
4 months of treatment	126	10.8
5 months of treatment	93	9.1
6 months of treatment	103	8.5
7 months of treatment	96	7.1
Normal value	≤ 70	≤ 5

Table 5 Case 5 (T.O. 58 years, male, colorectal cancer with liver metastasis

Test item / Time of treatment	GPT (IU/l 37°C)	TK activity (U/l)
Before treatment	135	8.2
1 month of treatment	71	5.1
2 months of treatment	64	4.8
3 months of treatment	91	5.0
4 months of treatment	88	5.2
Normal value	Male ≤ 75	≤ 5

3. Case 3 (F.M., 71 years, female, liver cancer)

The patient received treatment at another hospital, but the result was poor and jaundice appeared. She requested immunotherapy and visited our hospital on May 31, 2002. For hepatic tumor markers, α-FP slightly decreased at 3 months of treatment, but CA19-9 and PIVKA-II tended to increase. At 6 months and 1 year of treatment, however, CA19-9 and PIVKA-II decreased, clinical symptoms improved, and jaundice disappeared. The result for immunity (TK activity) was good (**Table 3**).

BioBran/MGN-3 was given for a total of 392 days.

4. Case 4 (H.H., 76 years, female, lung cancer)

The patient had treatment for cancer at another hospital, but obtained no improvement and visited our hospital on September 26, 2003.

The cancer was an adenocarcinoma which had spread throughout both lung fields.

The lung tumor marker (TPA) tended to decrease at 1 month of treatment, but slightly increased at 2 and 3 months and began to decrease again at 4 months. Coughing decreased at the same time. The immunocompetence (TK activity) has gradually increased (see **Table 4**).

BioBran/MGN-3 was ingested for a total of 128 days.

5. Case 5 (T.O., 58 years, male, colorectal cancer with liver metastasis)

The patient underwent surgery for colorectal cancer at another hospital, but liver metastasis occurred. He wanted to receive immunotherapy and visited our hospital on August 16, 2003.

Liver function (GPT) began to improve rapidly at 1 month of treatment. After that, good values were obtained at 2, 3, and 4 months. Immunocompetence (TK activity) stabilized after 1 month of treatment (**Table 5**).

Currently, he has no subjective symptoms and continues to work.

BioBran/MGN-3 was administered for a total of 77 days.

Discussion

The following points conclusions drawn from changes in general conditions, immunocompetence, and tumor markers in these 5 cases.

1) The therapeutic effect of the immunotherapy appears at 1 month of treatment in some cases and at 2 years in other cases. The appearance of the therapeutic effect differs largely between individuals. This means that it is important to continue immunotherapy with patience.
2) This therapy caused no adverse reactions in any of the 5 cases. Many patients suffer from serious adverse reactions to anticancer drugs. Large doses of radiotherapy also cause adverse reactions and considerable suffering to patients. Surgical removal of organs may make the patient's life difficult.
Therefore, it is preferable that patient-friendly immunotherapy be used as a main treatment for cancer.
3) For planning treatment of cancer, it is important to observe the patient's disease state from the 3 viewpoints of general condition, immunity, and tumor markers.

In case 1, the patient underwent treatment for 1 year or more at the department of surgery in a foundation hospital, but the attending physician recommended discharge because "there was no further treatment option and he had about 1 month of life remaining." He visited our hospital and received my immunotherapy. As a result, he is still working (having entered his 7th year of immunotherapy). This indicates the clinical significance of immunotherapy.

The safety of BioBran/MGN-3 can be easily imagined, because it is extracted from rice bran. The present clinical studies confirmed the safety of BioBran/MGN-3. Although the overproduction of rice has been a concern in Japan in recent years, it is advisable to produce more and use BioBran/MGN-3 not only in the treatment, but also in the prevention of cancer. The Ministry of Agriculture, Forestry, and Fisheries should make an administrative effort.

Conclusion

The author used the oral ingestion of BioBran/MGN-3 combined with BRP infusion as immunotherapy in the treatment of cancer patients, and good clinical effects and test results (tumor marker and immunity) were obtained.

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III-2-1

The Oral Administration of the Modified Arabinoxylan from Rice Bran (HRB) Prevents a Common Cold Syndrome in Elderly People Based on Immunomodulatory Function

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Key words: Hydrolysis rice bran, Arabinoxylan, Common cold syndrome, Immunomodulatory function

Abstract

The preventive effect of RIBEX against the common cold syndrome was examined in elderly individuals. RIBEX, containing the arabinoxylan derivative Hydrolysis Rice Bran (HRB), was prepared from the water soluble dietary fiber fraction of rice bran through partial processing using the carbohydrate complex of *Lentinus edodes* mycelia (shiitake). Using the non-chemically and non-biologically, treated water soluble fraction of Rice Bran (RB) as control, the examination was conducted in a cross-over double blind manner over an administration period of 6 weeks for each material. Fifty elderly persons who resided in a care

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institution under Japan's Long-term Care Insurance participated in this study. The results of 36 participants who showed comparative data in both terms were analyzed statistically. The most popular reason for withdrawal from the study was "leaving from the institution by a care contract". There was no withdrawal due to side effects of test foods. We observed symptoms such as "cough", "fatigue", "fever", "sore throat", "sputum", "nasal signs", and "sore breast", and assessed them based on the judgment of the medical staff. Although thirteen participants (36.1%) experienced at least one symptom in both groups, the total scores were of significantly higher value ($p<0.05$) in the RB group. The average duration in which the participants experienced symptoms was 2.6 days with RB compared with 1.2 days with HRB, which was not statistically significant. While there are many reports that HRB increases NK cell activity, no significant data was observed in this study because the participants had enough NK cell activity from the start.

HRB shortened the duration of the symptoms, reduced the necessity of symptomatic therapy, and was useful for the reduction of physical burden of acute respiratory tract infection.

Introduction

Carbohydrates, one of the main nutrients contained in food, consist of sugar, an energy source, and dietary fiber. The dietary fiber is barely digested or absorbed, but has a wide variety of physiological functions. Among them, the immunomodulatory function of the cell wall components of plants, microorganisms, and fungi have been reported by many researchers. β-1,3-Glucan from shiitake and suehirotake mushrooms has been used in clinical practice as an immunomodulatory agent.[1] Approval has been given to display the beneficial effects of several kinds of dietary fibers on the labels of foods containing them, e.g. inhibiting excessive increase in blood glucose, lowering serum cholesterol, and regulation of intestinal function. This approval is based on the labeling of foods for specified health uses in the system of foods with health claims, notified by the Pharmaceutical and Food Safety Bureau, MHLW, in 2001.

Rice bran, the residue left after polishing rice, contains a component that forms the cell wall skeleton for rice seed coats. Hydrolysis Rice Bran (hereafter called HRB) has been developed for use as a food product, and is closely related to the rice bran eaten by Japanese people from ancient times. The material for HRB, water-soluble dietary fiber extracted from rice bran, contains arabinoxylan as the main component. Different from β-1,3-glucan from mushrooms, arabinoxylan has a relatively low molecular weight even though it has a complex structure. RIBEX, produced by Daiwa Pharmaceutical Co., Ltd. is a granular food product containing HRB obtained by partially hydrolyzing the rice bran water-soluble fraction with many of the glycosidases contained in shiitake mushrooms.

Many researchers have reported that HRB has an immunomodulatory effect in man[2-7]. Other effects reported include active-oxygen elimination[8], sugar metabolism improvement[9], and a reduction in the adverse effects of some chemicals[10] that have been reported as functions of dietary fiber. These reports suggest that orally ingested HRB usually exerts a positive effect. RIBEX, containing HRB and which boosts the human immune system, promises to help maintain and improve health.

The common cold syndrome is caused by viruses frequently encountered in daily life. There is no specific remedy and the only option is to wait for natural recovery to occur[11]. When an influenza epidemic is expected, however, it is important to give influenza vaccine to high risk populations such as children and the elderly to prevent influenza itself and secondary infection by bacteria[11]. The risk of

community-acquired pneumonia, which sometimes occurs secondarily when the common cold syndrome is exacerbated, is known to be high amongst individuals aged 75 or over[12]. The risk of pneumonia is further increased in elderly patients with neurologic disorders, who are at higher risk of aspiration[13]. It was reported that a decrease in activity of daily living (ADL) leads to decreased immunity in the elderly with low T-cell mediated cellular immunity[14].

We studied the clinical usefulness of oral HRB based on its imunomodulatory effect in the prevention of common cold syndrome in the elderly who have low resistance due to decreased immune function. Although RIBEX is a food, this study was conducted in accordance with Good Clinical Practice.

Materials and Methods

(1) Subjects: Subjects were elderly people, without markedly impaired health, who stayed at a care facility for the elderly, Atreyu Uozaki, in Kobe City, Hyogo between January 2002 and March 2002 and who gave their consent to participate in this study. If at any time, subjects refused to take the study product or undergo the necessary tests, they were withdrawn from the study and the food product discontinued. When the attending physician judged that continuing the study might adversely affect a subject's health or was rendered impossible because the subject suffered an accident or fell ill or the subject left Atreyu Uozaki, the subject was withdrawn from the study and the food product discontinued.

(2) Food product ingested: The study food was RIBEX, whose principal constituent is the partially hydrolyzed water-soluble dietary fiber HRB. The control was a food the main component of which was a water-soluble extract of rice bran that is the raw material for HRB and is not hydrolyzed (hereafter called RB). Both foods were granular and sealed on three sides in an identical aluminum-foil film. They could not be identified. For both foods, the necessary amount for all subjects was prepared for every ingestion period. RB, a water-soluble extract, contained no chemically or biotechnologically treated water-soluble dietary fiber. The taste was the same for RB and HRB and both were rice bran derived foods. These are the reasons for choosing RB as the control. The ingestion dose of HRB was 500 mg/day because this is the dose expected to have an immunomodulatory effect based on our experience. The ingestion duration was 6 weeks, which was the shortest period necessary to ascertain any change in immune functions and common cold syndrome conditions. The study used a cross-over method, namely each subject ingested both foods for 2-week intervals. The subjects took the foods prepared by the facility personnel, who helped subjects to take the foods if necessary.

(3) Subject's living conditions: The daily environment and conditions of care for subjects were maintained in the same way as usual. The study was conducted in a double blind manner to eliminate observer bias. All subjects and facility staff members were blinded to the allocation of foods until the completion of the study.

(4) Examination and observation: Subject's background data were initials, date of birth, recent changes in body weight, complications during present treatment, history of respiratory disorders, height, and normal body temperature. To establish normal body temperature, each subject's temperature was measured over 2 weeks before the start of the study (if an abnormal temperature was noticed because of colds, etc., measurement was conducted in another period) and the median for the measurements was used.

Biomarkers, measured during the study were common cold symptoms (onset and disappearance) and

immune parameters such as NK cell activity. For fever, the highest temperature on each day was compared with the normal temperature and the difference was evaluated as 3 grades (No symptom, 1 Mild, 2 Moderate, and 3 Severe). "No symptom" meant a difference within 1°C between the highest and normal temperatures, "Mild" a difference of 1°C or more, "Moderate" a difference of 1°C or more and medical treatment given for the fever (such as cooling and antipyretics), and "Severe" where the highest body temperature exceeded 39°C. Common cold symptoms observed included typical general conditions (headache, malaise, myalgia, chills, and diaphoresis) and respiratory symptoms (cough, running/stuffy nose, sore throat, and chest pain)[15]. Each symptom was rated according to its worst manifestation on the day using 3 grades (No symptom, 1 Mild, 2 Moderate, and 3 Severe). "No symptom" meant the absence of symptoms, "Mild" the presence of mild symptoms but no need for symptomatic treatment, "Moderate" the presence of symptoms needing clinical observation and symptomatic treatment, and "Severe" indicated serious symptoms. Physicians and medical staff members at the facility, who were unaware of the food allocation, observed these items and recorded the results. For biomarkers other than cold symptoms, laboratory tests including hematology, blood biochemistry, and immunological tests, conducted before and after each ingestion period. All laboratory tests were performed by S R L Co., Ltd.

(5) Evaluation: Background factors were age, sex, height, body weight, BMI, and normal body temperature, for which basic statistics were calculated. For common cold symptoms (fever, headache, malaise, chills, cough, sputum, running/stuffy nose, sore throat, and chest pain), if a subject had one or more symptom, the duration for which the symptom persisted (duration of symptoms) was recorded. In addition, the severity of each symptom was scored ("No symptom" = 0, 1 "Mild" = 1, 2 "Moderate" = 2, and 3 "Severe" = 3). All scores were summed for each subject and the total was divided by the number of days of ingestion to obtain the "cold symptom score." Changes in cold symptoms, physical findings, and laboratory test values were analyzed by ingestion period and by study food. Abnormal findings were displayed in a summary table.

Results

1. Patient background

Subjects were 50 individuals staying at a care facility for the elderly, Atreyu Uozaki, in Higashinada, Kobe City in January 2002 and who gave their consent to participate in this study. Dropouts occurred due to the long study period and leaving the facility for reasons other than changes in health and physical condition. A total of 48 subjects took HRB in either period (HRB group) and 38 subjects took RB (RB group). No subjects withdrew from the study because of adverse reactions to the study food. 36 subjects completed both ingestion periods, providing data that allowed comparison in the same subject to be made (comparison subjects).

No subjects drank alcohol habitually but 4 reported smoking.

Tables I and **II** show background factors. As correct heights could not be measured in many subjects because of spinal deformity, heights were taken as reference values in addition to BMI. The normal body temperature was between 36 and 37°C in almost all subjects with no wide variation. Statistical analysis (significant level: $p<0.1$) showed no significant difference in age, height, body weight, or body temperature among all subjects and comparison subjects, suggesting no marked difference in backgrounds between both groups. The incidence of the most common complications was similar for both groups. These suggested

that there was no change in background factors in subjects, although the number of subjects changed after enrollment.

2. Changes in cold symptoms

The actual to planned (42 days) ingestion periods, duration of cold symptoms, proportion of subjects with common cold symptoms, and cold symptom scores were expressed as the mean ± standard deviation. **Table III** shows results for subjects given HRB and RB respectively. The number of subjects given RB was smaller than that receiving HRB and the ingestion period shorter for the former group. The incidence of cough, malaise, body temperature, and sore throat were high in both the RB and HRB groups. The duration of common cold symptoms was shorter for the HRB group than for the RB group. The number of subjects with one or more symptoms was similar for both groups, being 21 (43.8%) for the RHB group and 15 (39.5%) for the RB group. The total score for common cold symptoms was higher for the RB group and the scores for frequent cough, malaise, and fever were also higher for the RB group, although the score for nasal symptoms was lower. These results showed the lower severity of common cold symptoms in the HRB group.

Table IV and **Fig. 1** show changes in common cold symptoms in 36 comparison subjects who completed the HRB and RB ingestion periods. The ingestion period was almost the same for HRB and RB ingestions in the 36 comparison subjects. These subjects showed almost the same profile for common cold symptoms as the 50 subjects. The incidence of cough, malaise, fever, and sore throat were similar for both HRB and RB groups. The number of subjects with one or more symptoms was 13 (36.1%) for the HRB group and 13 for the RB group. However, the duration of symptoms was 1.2 days for the HRB group and 2.6 days for RB ingestion, although no significant difference was observed. The total symptom score was significantly higher for the RB group than for the HRB group ($p=0.0426$). For individual symptoms, the scores of frequent cough, malaise, and fever were higher for the RB group, but without a significant difference.

Table I Background of elderly subjects

Group		Total	HRB & RB	HRB	RB
n		50	36	48	38
gender	Male	15	9	15	9
	Female	35	27	33	29
	Ratio (M / F)	0.43	0.33	0.45	0.31
Age (years)	Min－Max	70 - 95	70 - 95	70 - 95	70 - 95
	Mean ± S.D.	84 ± 6.3	84 ± 7.2	84 ± 6.4	84 ± 7.1
Height (cm)	n	29	26	28	27
	Min－Max	132 - 165	132 - 165	132 - 165	132 - 165
	Mean ± S.D.	149 ± 8.0	149 ± 8.2	149 ± 8.2	148 ± 8.0
Weight (Kg)	n	43	36	41	38
	Min－Max	29 - 70	30 - 58	30 - 61	29 - 70
	Mean ± S.D.	43.8 ± 9.39	43.0 ± 7.76	43.6 ± 8.36	43.3 ± 9.05
BMI	n	29	26	28	27
	Min－Max	13.2 - 32.4	13.2 - 26.9	13.2 - 27.6	13.2 - 32.4
	Mean ± S.D.	20.1 ± 4.30	19.2 ± 3.31	19.6 ± 3.65	19.7 ± 4.12
BT (℃)	n	48	36	47	38
	Min－Max	36.2 - 37.1	36.2 - 36.9	36.2 - 37.1	36.2 - 36.9
	Mean ± S.D.	36.5 ± 0.21	36.5 ± 0.21	36.5 ± 0.21	36.5 ± 0.21

Total, all subjects participated in the clinical trial; HRB & RB, subjects administered both HRB and RB according to the plan; HRB, subjects administered HRB at least; RB, subjects administered RB at least.

Table II Background of elderly subjects –Major concomitant syndrome

Major concomitant syndrome	Total	HRB & RB	HRB	RB
Dementia	22 (44.0 %)	18 (50.0 %)	22 (45.8 %)	18 (47.4 %)
Sequela of Cerebral infarction	20 (40.0 %)	13 (36.1 %)	19 (39.6 %)	14 (36.8 %)
Subcapital fracture	12 (24.0 %)	12 (33.3 %)	12 (25.0 %)	12 (31.6 %)
Hypertension	10 (20.0 %)	4 (11.1 %)	9 (18.8 %)	5 (13.2 %)
Congestive Heart failure	8 (16.0 %)	4 (11.1 %)	7 (14.6 %)	5 (13.2 %)
Spondylitis deformans／Osteoporsis	6 (12.0 %)	5 (13.9 %)	6 (12.5 %)	5 (13.2 %)
Osteoarthritis	6 (12.0 %)	5 (13.9 %)	5 (10.4 %)	6 (15.8 %)
Gastriointestinal tract ulcer	5 (10.0 %)	3 (8.3 %)	5 (10.4 %)	3 (7.9 %)
Diabetes mellitus	5 (10.0 %)	3 (8.3 %)	4 (8.3 %)	4 (10.5 %)

Values are number of subjects observed concomitant syndrome(observed rate %). Total, all subjects participated in the clinical trial; HRB & RB, subjects administered both HRB and RB according to the plan; HRB, subjects administered HRB at least; RB, subjects administered RB at least.

Table III Comparison of the common cold cyndrome (CCS) conditions treated with HRB compared to RB in all Subjects participated in the study

Group	HRB		RB	
n	48		38	
Duration of administration(days)	38.4±9.55		30.8±18.10	
Observation term of CCS (days)	1.8±3.86		2.4±5.80	
CCS symptom	n (%)[1]	Score[2]	n (%)[1]	Score[2]
Cough	12 (25.0 %)	0.0344±0.10578	12 (31.6 %)	0.0742±0.15143
Malaise	7 (14.6 %)	0.0234±0.10012	10 (26.3 %)	0.0649±0.17966
Fever	9 (18.8 %)	0.0202±0.09985	7 (18.4 %)	0.0548±0.17805
Sore throat	5 (10.4 %)	0.0089±0.02890	5 (13.6 %)	0.0207±0.06018
Sputum	3 (6.3 %)	0.0040±0.01653	3 (8.3 %)	0.0038±0.01301
Nasal discharge / Sneezeing	6 (12.5 %)	0.0094±0.03017	3 (8.3 %)	0.0028±0.01034
Chills	2 (4.2 %)	0.0010±0.00481	1 (2.6 %)	0.0006±0.00386
Sore breast	0		1 (2.6 %)	0.0006±0.00386
TOTAL	21 (43.8 %)	0.1013±0.32429	15 (39.5 %)	0.2225±0.48250

Values are mean ± S.D. HRB, subjects administered HRB at least; RB, subjects administered RB at least.
The study was planned as a crossover method in which subjects take both foods in turn for a term of six weeks. Above are the groups with the observations for each and their evaluations.
1) : Number of subjects observed CCS symptom(observed rate %)
2) : The score was calculated by the following methods. The medical stuff recorded the worst condition of each CCS symptom once a day. Zero point CCS symptoms was not observed. When any condition was observed, one point was considered as slightly worse, two points required symptomatic therapy, and three points was considered as a serious phenomenon. However, a serious event was not seen in the study. These were integrated according to the observed term and it was divided by the duration days individually.

Table IV Comparison of the common cold syndrome (CCS) comditions of 36 subjects treated with HRB compared to RB in both HRB and RB administration according to the plan

Group	HRB		RB		HRB vs RB[3]
Duration of administration (days)	41.6±1.78		41.1±4.08		–
Observation term of CCS (days)	1.2±2.20		2.6±5.94		p = 0.2721
CCS symptom	n (%)[1]	Score[2]	n (%)[1]	Score[2]	HRB vs RB
Cough	7 (19.4 %)	0.0180±0.04778	10 (27.8 %)	0.0501±0.11160	p = 0.0626
Malaise	2 (5.6 %)	0.0079±0.03367	8 (22.2 %)	0.0423±0.15070	p = 0.0506
Fever	5 (13.9 %)	0.0040±0.01065	5 (13.9 %)	0.0377±0.15382	p = 0.0702
Sore throat	3 (8.3 %)	0.0053±0.01897	4 (11.1 %)	0.0185±0.05945	p = 0.1003
Sputum	1 (2.8 %)	0.0013±0.00794	2 (5.6 %)	0.0026±0.01106	p = 0.1116
Nasal discharge / Sneezeing	5 (13.9 %)	0.0119±0.03439	2 (5.6 %)	0.0015±0.00633	p = 0.2855
Chills	1 (2.8 %)	0.0007±0.00397	1 (2.8 %)	0.0007±0.00397	p = 0.9680
Sore breast	0		0		–
TOTAL	13 (36.1 %)	0.0491±0.09083	13 (36.1 %)	0.1535±0.38591	p = 0.0426*

Values are mean ± S.D. HRB, observations in term of administered HRB; RB, observations in term of administered RB.
The study was planned as a crossover method in which subjects take both foods in turn for a term of six weeks. Above are the observations of 36 subjects for which both terms can be evaluated.
1) : Number of subjects observed CCS symptom(observed rate %)
2) : The score was calculated by the following method. The medical stuff recorded the worst condition of each CCS symptom once a day. Zero point CCS symptoms was not observed. When any condition was observed, one point was considered as slightly worse, two points required symptomatic therapy, and three points was considered as a serious phenomenon. However, a serious event was not seen in the study. These were integrated according to the observed term and it was divided by the duration days individually.
3) : It evaluated by paired t test. * $p < 0.05$

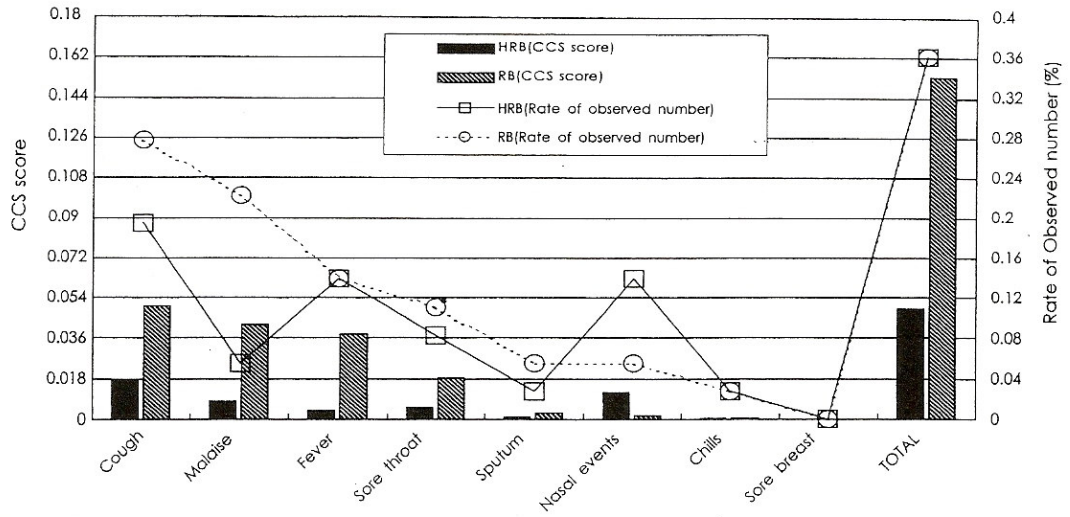

Fig. 1 Comparison of the common cold syndrome (CCS) conditions of 36 subjects treated with HRB compared to RB in both HRB and RB administered according to the plan

Table V Laboratory tests changes

Items	Normal range	HRB		RB	
		Baseline	After	Baseline	After
Total serum protein	6.6-8.4 (g/dL)	6.7±0.51	6.85±0.37	6.85±0.43	6.81±0.38
Serum albumin	3.5-5.2 (g/dL)	3.75±0.30	3.80±0.33	3.84±0.32	3.79±0.31
A/G rate	1.1-2.0	1.31±0.23	1.27±0.24	1.31±0.24	1.29±0.25
Blood urea nitrogen	8-20 (mg/dL)	22.44±6.2	22.15±5.9	22.23±6.5	21.56±5.9
Serum creatinine	0.7-1.5 (mg/dL)	0.95±0.19	0.95±0.18	0.96±0.20	0.93±0.21
Serum total choresterol	130-219 (mg/dL)	196±34	200±33	196±30	200±34
Serum HDL-choresterol	M: 38-72 (mg/dL) F: 43-77 (mg/dL)	49.13±11.62	49.23±11.89	51.87±13.06	49.71±12.33
Serum trigliseride	50-150 (mg/dL)	141±55	164±84	126±56	140±62
Alkaline phosphatase	100-350 (IU/L)	295±76	316±94	298±77	318±89
Cholinesterase	100-240 (IU/L)	125±29	129±31	126±28	128±31
Asparate aminotransferase (AST)	8-40 (IU/L)	18.4±5.3	19.9±8.0	18.4±6.6	18.5±6.4
Alanine aminotransferase (ALT)	5-43 (IU/L)	12.6±6.9	14.8±10.9	12.8±9.0	12.9±9.4
Lactate dehyrogenase	210-470 (IU/L)	338±57	351±100	336±56	357±145
γ -Glutamil transpeptidase	M: <70 (IU/L) F: <35 (IU/L)	16.5±7.3	17.8±7.6	17.3±7.5	16.8±6.4
Leukocyte alkaline phosphatase	30-80 (IU/L)	45±8.5	44.8±8.6	45.4±8.8	44.1±9.0
Vitamin A	431-1,041 (ng/mL)	428±102	451±96	411±121	445±99
Vitamin E	0.75-1.41 (mg/dL)	1.106±0.304	1.104±0.285	1.153±0.315	1.155±0.291
Vitamin B12	233-914 (Pg/mL)	451.4±254.1	443.4±349.6	468.1±323.5	414.7±241.4
Folic acid	2.4-9.8 (ng/mL)	8.46±3.69	9.00±4.77	8.17±4.24	8.87±3.43
Serum Zn	64-111 (μg/dL)	60±10	63±11	62±9	60±9
Serum Cu	70-132 (μg/dL)	118±19	117±23	123±22	120±17
Serum Mg	1.9-2.5 (mg/dL)	2.43±0.32	2.38±0.31	2.37±0.23	2.44±0.28
Serum Fe	M: 80-180 (μg/dL) F: 70-160 (μg/dL)	58.45±20.0	60.58±20.4	62.06±26.0	60.06±21.1
Transferrin	190-320 (mg/dL)	212±43	218±42	207±41	211±37

Values are mean ± S.D. HRB, subjects administered HRB at least; RB, subjects administered RB at least. Difference from baseline was evaluated by paired t test. * $p< 0.05$

Table VI Laboratory tests changes

Items	Normal range	HRB		RB	
		Baseline	After	Baseline	After
Leucocyte count	4000-9000 (/mm³)	6371±1770	6374±2386	5997±2035	6310±2042
Erythrocyte count	M: 420-570 (X10⁴/mm³) F: 380-510 (X10⁴/mm³)	385.9±41.8	392.8±46.0	392.3±38.6	390.4±41.7
Hemoglobin	M: 13.5-18 (g/dL) F: 12.0-16 (g/dL)	11.42±1.17	11.58±1.54	11.65±1.24	11.55±1.29
Hematocrit	M: 39-52 (%) F: 34-46 (%)	35.2±3.1	36.1±4.2	36.1±3.4	35.9±3.4
Neutrophil	40-71 (%)	67.0±9.3	66.9±8.3	66.6±7.9	68.5±8.4
Eosinophils	0-7 (%)	3.0±1.9	2.8±2.2	2.8±1.7	2.9±2.0
Basophils	0-1 (%)	0.6±0.3	0.6±0.3	0.7±0.3	0.6±0.3
Lymphocytes	27-47 (%)	25.6±7.9	25.6±6.4	25.9±6.6	24.3±7.0
Monocytes	2-8 (%)	3.8±1.6	4.2±1.5	4.1±1.3	3.8±1.3
platelets	13-35 (X10⁴/mm³)	22.3±7.1	22.8±7.8	22.5±7.8	21.8±7.4
C-reactive protein	<1.0 (mg/dL)	0.8±1.4	0.7±1.2	0.9±1.8	0.6±1.3
α 1-acidglycoprotein	42-93 (mg/dL)	93.1±30.9	88.3±32.3	95.9±39.0	90.2±29.8
NK cell activity	(%)	36.9±17.0	36.4±15.7	38.8±16.1	38.8±18.7
neutrophil phagocytosis function	70-87 (%)	79.6±8.4	80.2±8.4	76.5±10.2	79.5±9.5
lymphocyte blastgenesis, mitogensPHA	41000-79900 (cpm)	54605±17372	50487±15897*	47470±20582	37146±20506*
lymphocyte blastgenesis (control)	180-660 (cpm)	298±189	367±221	337±205	400±142

Values are mean ± S.D. HRB, subjects administered HRB at least; RB, subjects administered RB at least. Difference from baseline was evaluated by paired t test. * $p< 0.05$

3. Safety

No subjects given HRB and/or RB showed changes in symptoms or laboratory test values. Among the 36 comparison subjects, 31 underwent planned laboratory tests. **Tables V** and **VI** show changes in laboratory test values (mean ± standard deviation) in these subjects. A significant decrease before and after ingestion was observed in PHA stimulated lymphocyte blastogenesis ($p<0.05$). All other changes in laboratory test items were minor and showed no consistent trend.

The test values for PHA stimulated lymphocyte blastogenesis decreased for the ingestion of both foods but the degree of decrease was greater for RB than for HRB, and the difference was statistically significant. There was no difference in NK cell activity before and after either HRB or RB ingestion.

Discussion

The common cold syndrome is caused by viruses frequently encountered in our daily life. There is no specific remedy and the only rational approach is to treat symptoms, observe the clinical course, and wait for host's own immune system to effect healing naturally[11]. Some causal viruses are transmitted via air or in droplet spray from the infection source and thus isolation and protection are difficult. To prevent an epidemic and to stop infected patients from getting worse, it is important to improve immunity by various methods including vaccination, and medical agencies should take adequate measures to see that these measures are implemented. Vaccination priority is given to populations with low immunity, including immunologically naïve children and elderly people with decreased immunity[12,13]. Cellular immunity, mainly

mediated by T cells, is low in the elderly and it is reported that decreased activity of daily living (ADL) leads to decreased immunity in the elderly[14]. For the elderly at high risk of common cold syndrome and its more serious sequelae, it is important to prevent common cold syndrome by increasing resistance.

The clinical usefulness of RIBEX containing HRB was examined in infection with the common cold syndrome. A series of symptoms that starts with viral infection are caused by the immune response reactions and respiratory clearing mechanism and thus it is appropriate to use observations of these symptoms as indicators of the immunomodulatory effect of HRB[15]. Immunity tests were also included, based on previous studies of HRB.

RIBEX, a food product containing HRB, is produced by Daiwa Pharmaceutical Co., Ltd. It is a medicinally effective way of utilizing rice, which has long been the staple food of the Japanese people. HRB is a water-soluble dietary fiber derived from rice bran and contains partially hydrolyzed arabinoxylan. It has been reported to modulate immunity[2-7], scavenge active oxygen[8], improve sugar metabolism[9], and to reduce the adverse effects of some chemicals[10]. This study was conducted to evaluate the usefulness of HRB (that has an immunomodulatory function) in preventing common cold syndrome in elderly people with decreased immunity and resistance.

RB is a water-soluble extract from rice bran, containing a lot of dietary fiber and nutrients. Thus, it cannot be said to be a perfect placebo but we chose RB as the control food because the taste of HRB and RB are the same and both are rice bran derived foods.

Subjects were 50 elderly people, who were residents at Atreyu Uozaki, a care facility for the elderly and who gave their consent to participate in this study. Among them, 36 completed the necessary observations and tests for both periods of HRB and RB administration. The main reason for subjects discontinuing the study was leaving the facility. No subjects withdrew from the study due to adverse reactions to the study food. As there was no difference in background factors between all 50 subjects and the 36 comparison subjects, results for the 36 comparison subjects were compared and statistically analyzed.

The study was performed using the cross over method, where HRB and RB were given to the same subjects for 6 weeks each. The mean ingestion period for subjects including cases of discontinuation was 38.4 days for the HRB group (48 subjects) and 30.8 days for the RB group (38 subjects). In the 36 comparison subjects, the mean ingestion period exceeded 41 days. Subjects remained at the facility under ideal conditions that allowed the usefulness of the food to be properly evaluated. There was little variation in room humidity and temperature, the amount of exercise, and meals and the study period for both groups were roughly equal.

When the study was conducted, there was no epidemic of influenza in the district where the care facility was located, according to MHLW's infection trend survey. Influenza causes a severe fever and symptoms easily worsen and thus HRB may not have the same effect on influenza as seen in this study. Although the causal viruses of common cold syndrome were not specified in this study, the types of causal viruses may not have been numerous because the study was conducted within the same closed facility. In this study, common cold syndrome may have been caused by common cold viruses such as adenovirus and coxsackievirus that cause pharyngitis, coronavirus and rhinovirus that cause rhinitis and febrile inflammation, and parainfluenza virus and respiratory syncytial virus. All infections caused by these viruses have a similar clinical profile and it can be expected that HRB would produce the same effect as shown in this study.

If a multicenter study were to be conducted, planning and analysis would face a significant difficulty

because the difference between facilities in terms of background factors such as living conditions and the mode of infection spread have a considerable influence on clinical efficacy. Among common cold symptoms, cough, malaise, fever, and sore throat were more frequent in both food ingestion periods, reflecting acute immune reactions. These were followed by sputum and nasal symptoms. Almost no subjects complained of chest pain and there was no case of pneumonia secondary to worsened common cold syndrome. Symptoms were scored using 3 grades based on the results of evaluation by the physicians and medical staff at the facility. "Mild" (1 point) and "Moderate" (2 points) were differentiated according to the presence or absence of symptomatic therapy. "Severe" (3 points) indicated serious symptoms but no subjects had symptoms falling into this category. The duration of symptoms and symptom scores changed in a similar way in all 50 subjects and the 36 comparison subjects. In the 36 comparison subjects, the number of subjects with one or more symptoms was 13 (36.1%) in both ingestion periods but the total score for symptoms was significantly higher in the RB ingestion period ($p<0.05$). As the study food was given preventively, the number of subjects with symptoms should theoretically have been different between HRB and RB ingestions if the study food had a preventive effect on primary infection of the nasal membrane. However, no difference was observed between HRB and RB, but the total score for symptoms was different, suggesting that HRB acts on the expression and progression of symptoms after primary infection.

For individual symptoms, although the score for nasal symptoms was lower, those for cough, malaise, fever, and sore throat were higher in RB ingestion, but without a statistically significant difference. The duration of symptoms was 1.2 days for HRB ingestion and 2.6 days for RB ingestion. The difference in the symptom scores was more significant than the difference in the duration of symptoms between HRB and RB ingestions. The duration of the general symptoms of malaise and fever and the upper airway inflammatory symptoms, cough and sore throat, shortened in the HRB ingestion period. These results may have been obtained because HRB exerted an immunomodulatory effect and suppressed excessive inflammation. On the other hand, the score for nasal symptoms was higher for HRB ingestion. One possible explanation for this was that the subjects recovered the ability to discharge secretions from the upper airway and nasal membranes, which is associated with immune response and which is usually decreased in the elderly. In a clinical study on respiratory infection artificially induced by cold viruses, nasal symptoms were prominent, suggesting that cold viruses entered the body mainly through the nasal cavity. It was considered that HRB did not prevent primary infection itself but relieved cold symptoms by shortening the duration of symptoms and by decreasing the need for symptomatic therapy. HRB may have contributed to a reduction in the degree of physical stress during the acute phase of infection and prevented any worsening of the condition through a mechanism different from anti-inflammatory action.

In laboratory tests to monitor safety and changes in immune parameters, there was no clinically significant change before and after ingestion in any parameter, with the exception that PHA stimulated lymphocyte blastogenesis. No adverse reaction was observed. Thus, it was considered that HRB was safe. The PHA stimulated lymphocyte blastogenesis test is to induce the blastogenesis of T cells responsible for cellular immunity in the blood by the selective stimulator phytohemagglutinin (PHA) and to determine the degree of blastogenesis using DNA synthesis. Although elderly people have decreased cellular immunity, the degree of decrease was lower in the HRB ingestion phase during the study, suggesting the possibility that the T cell function might be normalized through the immunomodulatory effect of HRB.

There are many studies reporting that NK cell activity is increased by HRB ingestion[2,4,6]. However, no

significant change was observed before and after ingestion in the present study. One possible reason for this is that the NK cell activity was relatively high in our subjects: the mean value exceeded 30%. This may be because the subjects were adequately cared for under good nutritional, daily-environmental, and sanitary conditions. The NK cell activity decreased to under 20% in 6 subjects given HRB and 7 given RB, 3 of whom had a low value less than 10%. As mentioned above, however, an immunomodulatory effect was noticed. A further study is needed to elucidate the relationship with these immune parameters.

It has been reported that oral HRB has an immunomodulatory effect[2-7]. In the present study, HRB reduced common cold symptoms in subjects with adequate NK cell activity. This suggests that the effect of HRB may consist not only of enhancement of NK cell activity, as previously reported, but also stimulation of the entire immune system including humoral immunity or control of excessive expression of local and systemic physiological responses such as fluid secretion and fever.

The hydrolysis rice bran given orally, based on its immunomodulatory effect, shortened the duration of common cold symptoms and reduced the severity of symptoms and the need for symptomatic therapy in elderly subjects in this study. The hydrolysis rice bran was shown to be useful in the reduction of physical stress at the early stage of respiratory infection.

Conclusion

The preventive effect of RIBEX on common cold syndrome was studied in elderly people. RIBEX contains HRB, consisting of arabinoxylan derivatives produced by processing the water soluble dietary fiber extracted from rice bran with glycosidases contained in shiitake mushrooms. The control food was an extract from rice bran without chemical or biotechnological treatment. These foods were given for 6 weeks each in a double-blind cross-over manner. Subjects were 50 elderly people at a care facility for the elderly. A total of 36 subjects completed both ingestion periods and allowed comparison between HRB and RB in the same subject. The main reason for discontinuation was leaving the facility and there was no withdrawal because of adverse reactions. The symptoms of cough, malaise, fever, sore throat, sputum, nasal symptoms, and chest pain were observed by the medical staff in the facility and scored based on the medical staff's judgment. The number of subjects with one or more symptoms was 13 (36.1%) for both groups but the total symptom score was significantly higher for RB ingestion ($p<0.05$). The duration of symptoms was 1.2 days for HRB ingestion and 2.6 days for RB ingestion but no significant difference was observed. Although many researchers reported that HRB increased NK cell activity, no significant change was observed in this study possibly because our subjects had high NK activity before ingestion.

In conclusion, HRB shortened the duration of common cold symptoms and reduced the severity of symptoms and the need for symptomatic therapy, demonstrating its usefulness in reducing physical stress at the acute stage of respiratory infection.

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Experience with Administration of Modified Arabinoxylan from Rice Bran (BioBran/MGN-3) in Patients with Rheumatoid Arthritis

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Key words:
Rice Bran Arabinoxylan Derivative, Rheumatism, Supplementary Treatment, Inhibition of Inflammation

Abstract

The functional food, rice bran arabinoxylan derivative (BioBran/MGN-3), was administered over a long period to patients with rheumatoid arthritis given mainly symptomatic treatment with steroids, to evaluate its supplementary effect with representative treatments for rheumatism, such as steroids, analgesics, and thermotherapy. Steroids are essential for treatment of rheumatism, but it is desirable to minimize the dose, to avoid adverse reactions. In recent years, there have been many reports on the functions of food ingredients, including superoxide scavenging and biophylaxis improving actions. This study evaluated the efficacy of BioBran/MGN-3, a functional food material. BioBran/MGN-3 has been reported to have the effects of activating natural killer cells (NK cells) and inhibiting inflammation. The author confirmed and reported that it relieved cold symptoms in the elderly. The present study, where 8 patients with chronic rheuma-

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tism were given BioBran/MGN-3 for 6 to 12 months, demonstrated the improvement in symptoms and QOL, suggesting its effectiveness.

Introduction

Rheumatoid arthritis is an autoimmune disease, where the IgG and IgM autoantibodies, rheumatoid factors, are produced in synovial fluid in response to IgG and recognize each other to from IgM-IgG complexes, which induce inflammatory reactions. The immune complexes activate complement, which promotes tissue destruction by attracting polymorphonuclrear leukocytes and simultaneously activates basophils and platelets, stimulates release of histamine and serotonin, and increases vascular permeability, leading to further increase in immune complex deposition. Corticosteroids and nonsteroidal anti-inflammatory drugs are generally used in treatment of rheumatism. Immunosuppressants are also sometimes combined to inhibit the production of autoantibodies. Thus, patients are likely to experience adverse reactions. In this study, the rice bran arabinoxylan derivative (BioBran/MGN-3), a functional food with immunomodulatory and anti-inflammatory effects, was administered to evaluate its supplementary effect during treatment with steroids and analgesics.

Study Method and Clinical Courses

BioBran/MGN-3, a derivative of hemicellulose contained in the rice coat, is a biological response modifier (BRM) that mainly consists of polysaccharide composed of arabinose and xylose[1]. Eight patients with chronic rheumatism were administered BioBran/MGN-3 for 6-12 months to observe changes in their subjective symptoms and CRP and improvement in QOL. Five of 8 patients were on steroids and analgesics and the others on analgesics, chinese medicines, and thermotherapy.

The clinical courses of 3 patients who responded well to BioBran/MGN-3 will be reported below.

Case 1

1. Symptoms and treatments

A 78-year-old woman received regular treatment for osteolytic rheumatism from March 1998. The disease was classified as Stage IV in Class III by the Stein-Blocker classification.

The patient was orally given Predonine at 10 mg and Bucillamine at 200 mg/day as a symptomatic therapy. She had severe pain and walking difficulty, and bone destruction was progressive. Artificial joint replacement was recommended, but postponed on her wishes. After obtaining her consent, BioBran/MGN-3 was administered from April 17. She had severe pain in both hands and knees and the joints, slept poorly, and was almost bedridden. Serological test results were ++ for RA test, 65 IU/m*l* for RF, and 2.0 mg/d*l* for CRP. The dose of BioBran/MGN-3 was 1 g/day during the 1st week, 2 g/day for next 3 weeks, and 3 g/day after that.

2. Clinical course

Pain in the hands and feet were relieved at 1 week of BioBran/MGN-3 intake, and she was able to sleep well and walk using a walker. She had reduced pain in the knee and foot joints at 2 weeks and could walk with a cane at 1 month. In the serological test on October 5, the RA test result was +, RF 34 IU/m*l*, and

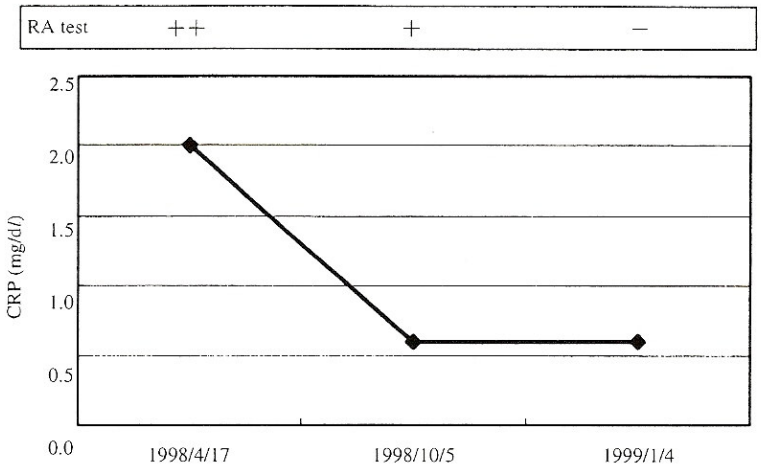

Fig. 1 Changes in CRP and RA test

CRP 0.6 mg/d*l*, and the steroid and DMARD were withdrawn. On January 4, 1999, the RA test was -, RF 14 IU/m*l*, and CRP 0.6mg/d*l*, and the disease followed a good course (the normal range for RF was≦20 IU/m*l*) (**Fig. 1**).

Case 2

1. Symptoms and treatment

A 77-year-old woman visited our clinic in March 2003. She had severe pains in the hand and foot joints, sleeplessness, and markedly reduced physical strength through decreased appetite. The disease was classified as Stage IV in Class III. The RA test result was +++, RF 500 IU/m*l*, and CRP 1.8 mg/d*l*. She was diagnosed as having typical rheumatism. The steroid Predonine at 10 mg and a DMARD were given combined with thermotherapy, but pain persisted without any benefit. Administration of BioBran/MGN-3 at 3 g/day was started on June 20, 2000, and continued for 1 year, after which the dose was decreased to 2 g/day. She receives the therapy until now.

2. Clinical course

Pain in the hands and feet was reduced after 3 days of administration of BioBran/MGN-3, and the patient was able to sleep and had increased appetite. At 3 months, pain in the hand and foot joints were further reduced, and she gained 2 kg. In late December at 6 months, the pain became endurable and test values improved: the RA test was ++, RF 62 IU/m*l*, and CRP 1.0 mg/d*l* . The steroid was withdrawn and only the DMARD was given. In June 2001, she still took BioBran/MGN-3 at 2 g/day and symptoms were stable.

Case 3

1. Symptoms and treatment

A 39-year-old woman visited our clinic on June 10, 2000. A diagnosis of rheumatism was made and she was given steroid Predonine at 15 mg, an analgesic, Chinese medicine, and thermotherapy. BioBran/MGN-3 was administered from October 5. The dose was 1 g/day during the 1st week, 2 g/day for the next 1

month, and 3 g/day after that. The RA test result was ++, RF 320 IU/m*l*, and CRP 1.6 mg/d*l*.

2. Clinical course

Coldness in her hands and feet was reduced after 3 days of administration of BioBran/MGN-3, and the frequency of pain decreased. The pain was further reduced at 1 week, and the analgesic was withdrawn. Facial and hand swelling were reduced in early November at 1 month. At 3 months, she had almost no pain and could sleep well. The RA test result was +, RF 92 IU/m*l*, and CRP 1.0 mg/d*l*. The dose of the steroid was decreased to half the previous level. She had no pain and could bend both middle fingers freely in April 2001 at 6 months.

Results and Discussion

BioBran/MGN-3 had a very good effect on 3 of the 8 patients. Subjective symptoms, especially pain, improved, and the RA index and CRP level decreased. The steroid was completely withdrawn in 2 patients, and the dese was decreased in the remaining one. Two other patients, in whom no very good effect was observed, had improved subjective symptoms. As a result, their QOL improved. The 3 remaining patients had neither improvement nor exacerbation in the 6-month administration period. Although symptoms were expected to worsen temporarily because of the immune-enhancing effect of BioBran /MGN-3, gradual increase of the dose caused no adverse reactions in any patient.

There are many reports of actions of BioBran/MGN-3. NK-cell activation (Ghoneum et al.)[2], anti-inflammatory effect on a rat asthma model (Endo et al.)[3], survival improvement in an LPS-induced sepsis model (Kubo et al.)[4], intestinal-membrane protection against anticancer drugs in mice (Jacoby et al.)[5], protection against anticancer drugs in mice (Endo et al.)[6] and resistance to drug-related hepatic impairment (Sanada et al.)[7]. From these, BioBran/MGN-3 could be suggested to be a functional food that enhances immunity and exerts a prophylactic effect based on the anti-inflammatory action. The authors conducted a double blind clinical study to evaluate the preventative effect of BioBran/MGN-3 on the common cold syndrome in elderly people who stayed in the author-managed care institution and confirmed the effect of symptomatic relief[8]. BioBran/MGN-3 showed the effect in a relatively short time in the patients in this study. These good results may have been because it exerted an anti-inflammatory effect on rheumatism and at the same time, enhanced immunity: it was reported that patients with rheumatism are generally immunocompromised because of decreased lymphocyte counts[9].

Conclusion

These results suggested the efficacy of BioBran/MGN-3 as a supplement therapy. The main mechanism of the action is considered relief of immunological inflammation. We propose to try this therapy further, because it caused no adverse reactions.

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