The Japanese MacroForce® Study in Cancer (IMMD/MFJ/001&002-Ph3)

Title: Beta-1,3-D-Glucan, its Immune Effect and its Clinical Use.

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Summary of two clinical trials

1) Cancer relapse after surgery (n=72), randomized, controlled

2) Survival in terminally-ill cancer patients (n=99), randomized, controlled

1. Introduction

It has been already shown that malnutrition makes patients susceptible and vulnerable to infection. As the immune system has become better understood and analyzed in details, the relevance between nutrition and immune state has been found to be more important than we had expected. Nutrition is involved in aging, allergy and host defense, as well as cancer and infection. Therefore, it is important that the various aspects of nutrition be considered in the treatment of each patient. We have seen many patients suffering from disorders such infections, cancer, hematological disorders, aging, chemotherapy, surgery, radiation, et cetera, who have a compromised immune system which is partially the result of malnutrition. It is important, therefore, that in patients with a compromised immune system, the improvement of immune function be a priority.

2. Methods

In the first trial the effect of beta-1,3-D-glucan* (beta glucan) on the rate of cancer relapse was assessed in 49 post-surgical patients (breast cancer: 19, ovarian cancer: 8, cervical cancer: 22). All the patients were clinically evaluated with stage 2 cancer. Beta glucan was administered to 26 patients for seven days before and for 15 months after surgery. Each patient was treated with one capsule of beta glucan (2.5 mg/capsule) orally one hour before meals, three times a day; 23 received no treatment and served as controls.

In a second trial the effect of beta glucan on the survival of cancer patients was assessed in 99 post-surgical patients that had suffered relapse, were inoperable and were given 3 months or less to live. 54 of these patients were treated with 2 capsules of beta glucan three times a day (total dose of 15 mg/day) and 45 were not treated and served as controls. The beta glucan used in the studies above was purified from baker's yeast and manufactured by Immudyne (USA) [sold in Japan under the trademark of MacroForce®*]

**The beta 1,3-D-glucan used in this study and manufactured by Immudyne is actually Beta-1,3/1,6-D-glucan. It is referred to as Beta-1,3-D-glucan because of the small amounts (3-8%) of beta (1,6) bonds it contains. However, it is the small number of (1-6) bonds that confer biological activity to the molecule.*

3. Results

In the first trial a comparison of two groups showed that after surgery 5 patients out of 23 suffered relapse in the control group.

No relapse occurred in the patients treated with beta glucan during a 15-month follow-up (Table 1). Table 2 shows the time course of relapse during the 15-month follow-up. The beta glucan-treated group has now been followed for 20 months without any reoccurence.

Treatment	Cancer Type	# Patients	# Relapses
None	Breast Stage II	9	2 (8.7%)
	Ovarian Stage II	4	0
	Cervical Stage II	10	3 (13%)
Beta Glucan	Breast Stage II	10	0
	Ovarian Stage II	4	0
	Cervical Stage II	12	0

Table 1: Effect of Beta-1,3-D-Glucan on Relapse after Cancer Surgery

Treatment	Relapse	Time After Surgery (Months)				
		3	6	9	12	15
None	No	23	22	21	21	18
None	Yes	0	1	2	2	5 (22%)
Beta Glucan	No	26	26	26	26	26
Beta Glucan	Yes	0	0	0	0	0

Table 2: Effect of beta-1,3-D-Glucan on Cancer Recurrence after Surgery

In the second trial 65% (35/54) of the patients who received beta glucan survived more than 3 months and 43% (23/54) survived more than 6 months. In contrast, only 4.4% (2/45) of the untreated, control patients survived 3 months and none survived 6 months (Table 3).

Treatment	# Patients	Patients Surviving	
None	45	3 Mo.	6 Mo.
		2 (4.4%)	0
Beta Glucan	54	35 (65%)	23 (43%)

Table 3: Effect of Beta-1,3-D- Glucan on Survival of Terminal Patients

4a Immune Markers

Immune Markers	Before	1 Month	2 Months	3 Months
TNFg (14)	4.0	17.2	23.9	45.2
IL-12 (7.8)	8.7	15.4	24.2	41.5
NK cells (18-40)	15	22	26	64
LAK (20-80)	19	58	72	84
CD161	8.2	12.1	19.2	18.51
Three-color IFNg/IL-4(7)	0.27 4/14.7	1.61 17.2/10.7	19.9 23.9/1.2	41.1 45.2/1.1

4b. Tumor Markers

Tumor Markers	Before	1 Month	2 Months	3 Months
BCA 225 (160)	130	98	83	65
CEA (5)	18.3	6.3	4.5	3.1
TPA (70)	123	119	53	32
CA-15-3 (30)	56	41	35	23

Table 4: Effect of beta glucan on Immune Markers (a) and Tumor Markers (b) of a 48-year old woman with breast cancer Stage 1

5a Immune Markers

Immune Markers	Before	1 Month	2 Months	3 Months
TNFg (14)	12.3	43.5	84.2	142
IL-12 (7.8)	7.2	10.8	12.8	19
NK cells (18-40)	8	18	28	45
LAK (20-80)	15	22	48	76
CD161	7.6	11.5	18.8	20.5
Three-color IFNg/IL-4 (7)	40 12.8/3.2	18.1 43.5/2.4	56.1 84.2/1.5	

5b. Tumor Markers

Tumor Markers	Before	1 Month	2 Months	3 Months
LAP (500)	780	620	510	345
TPA (70)	780	430	72	44
CEA (25)	85	42	28	18
CA-199 (37)	110	56	42	32

Table 5: Effect of beta glucan on Immune Markers (a) and Tumor Markers (b) of a 62-year old man with stomach cancer Stage 2

4. Discussion

The anitviral, antitumor, anti-immaflatory effect, and macrophage activation activities of beta glucan have already been reported. Investigators in the United States have reported that macrophages have the receptor for beta-glucan, and that the binding of beta glucan to the receptor leads to the activation of macrophage. Subsequently, other immune cells such as neutrophils, NK cells, and B cell have been found to have the receptor and are activated by beta-glucan. Activated macrophages release IL-1, IL-12, IFN-gamma and a number of other cytokines that are involved in the activation of helper T cells. The phagocytosis of apoptotic cancer cells allows macrophages to present the cancer antigens to naive T cells (TO cells), the information is then conveyed to the helper T cells (TH1cells), and then to cytolytic T cells (CTL), which become activated. Activated macrophages also produce IL-1, which activates helper T cells, which in turn produce IL-2 and IFN-gamma. The increase of IL-1 and IL-12 induces killer T cells and natural killer cells to attack and destroy cancer cells. Macrophages then engulf the dead cells, thus reducing the tumor. The change in the immune markers and cancer markers in two patients treated with 15 mg beta glucan are presented in table 4 and 5.

5. Summary

In this study we have treated patients with breast, ovarian and cervical with 7.5 mg of beta glucan/day and found that in treated patients there was no recurrence of cancer, whereas in the non-treated group there was a recurrence rate of 22%. We also treated terminal cancer patients with 15 mg

beta glucan/day and demonstrated a decrease in mortality with time. In two cancer patients we measured various immune parameters and found that these increased with beta glucan treatment, whereas tumor markers decreased.

6. Literature

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