RESEARCH ARTICLE

Positive Effects of Oral β-Glucan on Mucositis and Leukopenia in Colorectal Cancer Patients Receiving Adjuvant FOLFOX-4 Combination Chemotherapy

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Abstract

   The present study aimed to determine the effect of oral β-glucan on mucositis and leukopenia in 62 consecutive patients with colorectal cancer treated with an adjuvant FOLFOX-4 regimen. The patients were retrospectively evaluated in 2 groups: one group received β-glucan and the other did not (control group). Leucocytes, neutrophils, and platelets were evaluated before and 1 week after chemotherapy and oral mucositis and diarrhea were noted. Leucocyte and neutrophil counts after chemotherapy in the β-glucan group were 7,300/mm^3 and 3,800/mm^3, respectively, and the reductions, as compared to baseline, were not significant (p=0.673 and 0.784). The median platelet count was 264,000/mm^3 after chemotherapy in the β-glucan group and the reduction, as compared to baseline, was borderline significant (p=0.048). In the control group, reduction in leucocyte, neutrophil, and platelet counts was statistically significant. Oral mucositis and diarrhea were less common in the β-glucan group. We conclude that β-glucan can be used to reduce the adverse effects of chemotherapy.

Keywords: β-glucan - chemotherapy - neutropenia - mucositis - colorectal cancer

Introduction

   A significant proportion of cancer patients receive complementary medical/herbal therapy while undergoing conventional anti-cancer treatment (McEachrane-Gross et al., 2006; Inglin et al., 2008; Mueller et al., 2008; Yang et al., 2008; Supoken et al., 2009; Nazik et al., 2011). β-glucans (1,3-1,6 β-D-glucan) were recently reported to be one of the active ingredients responsible for the immunomodulation of many of the herbs used in such therapy (Ooi VE, 2000; Vannucci et al., 2013). β-glucans are complex polysaccharides in the cell walls of yeasts, fungi, and pathogenic bacteria. β-glucans have been shown to act on several immune receptors, including Dectin-1, complement receptor 3 (CR3), and toll-like receptor (TLR)-2/6, and stimulated the production of macrophages, neutrophils, monocytes, natural killer cells, and dendritic cells in in-vitro studies (Chan et al., 2009). Thus, β-glucans may have antibacterial, immunomodulator, and anti-cancer effects. In addition, the effects of β-glucans as chemo-immunotherapeutic agents in a number of solid cancers have also been shown (Hazama, 2009; Akazawa et al., 2010; Harada et al., 2010; Nakagawa et al., 2010; Watanabe et al., 2013). There is a growing interest in the potential usefulness of β-glucans in limiting the side effects of chemotherapy and radiation therapy, particularly because β-glucans can be used not only as a therapeutic agent, but also as a prophylactic. Delaying chemotherapy cycles because of neutropenia and mucositis may reduce its effectiveness; therefore, it is important to minimize the side effects of chemotherapy with supportive therapy.

   The present study aimed to examine the effect of oral β-glucan on mucositis and leukopenia in a group of colorectal cancer patients with a high risk for neutropenia and mucositis who received adjuvant FOLFOX-4 (oxaliplatin, 5-fluorouracil, and folinic acid) combination chemotherapy.

Materials and Methods

   This retrospective study included 62 consecutive patients with colorectal cancer who underwent a FOLFOX-4 treatment regimen between July 2009 and July 2010. The ethics committee of Erciyes University approved the study design (project number: 494). The records of patients admitted with the diagnosis of colorectal cancer were reviewed consecutively. Those patients who had a chronic disease or had used agents

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(such as a herbal therapy or drugs) other than β-glucan that may affect immunity were excluded from the study. Sixty two patients who enrolled and signed informed consent forms were included in the study. The patients were divided into 2 equal groups. The treatment group included patients who had received pure preparation of β-glucan 50 mg/day for at least 1 week concomitant with the first cycle of chemotherapy, whereas the control group included patients who had received only chemotherapy. Leucocyte, neutrophil, and platelet counts were determined in both groups 1 day before (baseline) and 1 week after chemotherapy via the cell detection method, using a Siemens Advia 2120i hemogram device. Counts between 4800 and 10800/mm^3, 2200 and 4800/mm^3, and 130000 and 400000/mm^3 were considered normal for leucocytes, neutrophils, and platelets, respectively. The presence of oral mucositis and diarrhea in the patients was graded according to NCI-CTC toxicity criteria and noted.

SPSS v.15.0 software was used for statistical analysis. In both groups changes in leucocyte, neutrophil, and platelet counts and alterations in oral mucositis and diarrhea before and after chemotherapy were compared using the Wilcoxon and chi-square tests. A p value <0.05 was considered statistically significant.

Results

There were 21 male and 10 female patients in the treatment group, and the median age was 61 years (range: 43-72 years). The control group included 17 male and 14 female patients, and the median age was 55 years (range: 30-78 years). There were no statistical differences in age or gender between the 2 groups (p values >0.05). All of the patients had adenocarcinoma histology and stage III disease. The tumors did not include the rectum, and none of the patients had received radiotherapy.

Median leucocyte and neutrophil counts after chemotherapy were 7300/mm^3 and 3800/mm^3, respectively, in the treatment group (Table 1), and were not significantly different from the baseline values (p=0.673 and p=0.784). In the treatment group the median platelet count was 264000/mm^3 after chemotherapy, and the difference between the baseline value was significant (p=0.048) (Table 1). In the control group leucocyte, neutrophil, and platelet counts were significantly lower after chemotherapy (median values were 5600/mm^3, 2880/mm^3, and 229000/mm^3, respectively; p<0.01) than before chemotherapy (Table 1).

While none of the patients developed hematologic toxicity, except for grade 1 leukopenia in 1 patient in the treatment group, 6 patients in the control group had grade 1 leukopenia, 2 had grade 2 leukopenia, 3 had grade 1

Table 1. Median Leucocyte, Neutrophil, and Platelet Counts Before and After Chemotherapy

	Leucocytes/mm³ (before/after)	Neutrophils/mm³ (before/after)	Platelets/mm³ (before/after)
Treatment group	7740/7300	4400/3800	292000/264000
p values	0.673	0.784	0.048
Control group	7200/5600	4130/2880	311000/229000
p values	<0.01	<0.01	<0.01

Table 2. Non-Hematologic Toxicities After Chemotherapy in Two Groups

Non-hematologic toxicity, No. (%)	Side effects	Grade 1 (n)	2 (n)	3/4 (n)
Treatment group 6 (19)	Oral mucositis	1	2	0
	Diarrhea	2	1	0
Control group 13 (42)	Oral mucositis	4	2	0
	Diarrhea	3	3	1

neutropenia, 3 had grade 2 neutropenia, and 3 had grade 1 thrombocytopenia. In addition, oral mucositis and diarrhea secondary to chemotherapy were less common in the treatment group. Non-hematologic toxicity (all grades) was observed in 6 (19%) patients in the treatment group and in 13 (42%) patients in the control group (Table 2). Due to the limited number of patients, statistical analysis could not be done. There were no β-glucan-induced side-effects.

Discussion

The data on the immunomodulatory mechanisms of β-glucans which were obtained predominantly from animal studies, suggest that following oral administration, β-glucans, enter the small intestine and are captured and internalized by macrophages. B-glucans are then fragmented into smaller β-glucans and are carried to bone marrow and the endothelial reticular system. Then, the small fragments of β-glucans are released by macrophages and are taken up by circulating granulocytes and monocytes, and dendritic cells. The immune response will then be revealed (Chan et al., 2009; Torello et al., 2012). There is little to no evidence for these hypothesized mechanisms of action in humans. It is also suggested that β-glucans have no direct cytotoxic effects and do not trigger any apoptotic pathways in cancer cells (Chan et al., 2009); however, research has shown that β-glucans augmented antitumor monoclonal antibody-mediated efficacy via stimulation of the innate effector neutrophil complement receptor 3 (Zhong et al., 2009).

Clinical trials showed that β-glucans were well tolerated (Miyakoshi et al., 1984; Kawaoka et al., 2003) and provided some clinical benefit when added to adjuvant chemotherapy (Nakano et al., 1999). In a prospective clinical trial 23 female patients with advanced breast cancer were compared to 16 healthy female controls (Demir et al., 2007). Oral β-glucan was administered daily, and blood samples were collected on day 0 and 15. Oral β-glucan was reported to stimulate the proliferation and activation of peripheral blood monocytes in the patients with advanced breast cancer. Another study included 40 patients with head-neck tumors who were divided into 2 equal groups (Papila et al., 2004). Three courses of chemotherapy were administered to both groups and 1 group also received oral β-glucan (10mg/day or 20mg/day for patients weighing >60kg). Leucocytes were counted before chemotherapy and after 3 courses of chemotherapy. In the group that received oral β-glucan the decrease in leucocyte counts after chemotherapy was limited, whereas in the group that received chemotherapy alone

leucocyte counts decreased significantly. In addition, oral mucositis secondary to chemotherapy and radiotherapy was less common in the patients that received β-glucan. Similar to the results of the 2 above-mentioned studies, our study showed that leucocyte and neutrophil counts did not change significantly in the treatment group for 1 week during the first course of chemotherapy, as compared to baseline values. In addition, non-hematologic toxicity (diarrhea and oral mucositis) in the treatment group was less common and of lower grade than that in the control group. β-glucan was well tolerated in the treatment group, as was previously reported. Ina et al. (2011) evaluated 78 metastatic or recurrent gastric cancer patients receiving S-1-based chemotherapy as first-line treatment between 2004 and 2010. The chemotherapy alone group comprised 37 cases, and the group that received chemoimmunotherapy with lentinan (beta-1, 3-glucan) comprised 31 cases. In this study, showed that the median OS was significantly longer in the group who received chemoimmunotherapy with lentinan than in the chemotherapy alone group (p=0.0406), however the incidence and degree of adverse effects were no significant differences between patients who did and those who did not receive lentinan (Ina et al., 2011).

In a multi-center clinical study, 80 advanced colorectal cancer patients were orally administered superfine dispersed lentinan along with chemotherapy, and adverse events associated with chemotherapy and the patients' quality of life (QOL) were evaluated. Adverse events associated with chemotherapy developed in 9 of the 64 patients. Among the 48 patients assessed for QOL, those with a low QOL score before β-glucan treatment (n=23) had a significant improvement in QOL score following 12 weeks of β-glucan treatment. The researchers reported that superfine dispersed lentinan (beta-1,3-glucan) safely and effectively suppressed the adverse effects of chemotherapy, and improved the patients' QOL (Hazama et al., 2009). Similar studies conducted with gastric cancer patients reported that β-glucan combined with chemotherapy (from the initial period until the end of the course) improved QOL, and that there was a significant correlation between QOL and survival (Kataoka et al., 2009; Yoshino et al., 2010). It was not possible to assess the QOL in the present study; however, the observed lower frequency and lower grade of diarrhea and oral mucositis in the treatment group indicates that the QOL in this group was probably higher than that in the control group.

In conclusion, the present study shows that oral β-glucan 50mg/d, due to its effects on the immune system, may have lowered the risk of low QOL, interruption of chemotherapy cycles, and decreased effectiveness of chemotherapy by decreasing the incidence and severity of diarrhea, mucositis, and neutropenia in patients with a high risk for these conditions. Considering the present study's results and those previously reported, β-glucan co-administered with chemotherapy has positive effects on neutropenia and QOL in cancer patients. Large-scale prospective studies on β-glucan use with long-term follow-up are required to further delineate the beneficial effects of β-glucan and its potential effect on survival in cancer patients.

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