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ARAŞTIRMA / RESEARCH

Effect of prophylactic beta-glucan use on the incidence of neutropenic fever and survival rates in pediatric patients with sarcoma

Pediatrik sarkom hastalarında profilaktik beta-glukan kullanımının nötropenik ateş sıklığı ve sağkalım üzerine etkisi

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Abstract

Purpose: Some patients with cancer use herbal therapy as an adjunct while receiving conventional cancer treatments. Beta-glucans have direct cytotoxic effects on cancer cells as well as stimulatory effects on the immune system. In this study, a nutritional supplement containing 1,3-1,6 beta-glucan obtained from baker's yeast (Saccharomyces cerevisiae) was used by patients diagnosed with sarcoma, and this study aimed to retrospectively evaluate the effect of beta-glucan use on the incidence of neutropenic fever (NF) and survival rates.

Materials and Methods: Among the patients diagnosed with sarcoma between 2014 and 2017, 27 patients who used beta-glucan were included in the beta-glucan group, and 31 patients who did not use beta-glucan were included in the control group. The clinical records of patients were retrospectively analyzed.

Results: The number of patients who had NF and the mean length of hospital stay due to NF were higher in the beta-glucan group than those in the control group, but the results were not statistically significant. The overall survival rates at 5 years were 83.3% and 52.9% and event-free survival rates at 5 years were 48.1% and 71% in the beta-glucan and control groups, respectively.

Conclusion: The effect of prophylactic beta-glucan use on the incidence of NF and survival rates in pediatric patients with sarcoma should be evaluated more reliably in further prospective studies on a large patient group.

Keywords:. Beta-glucan, neutropenic fever, pediatric sarcomas, survival

Öz

Amaç: Kanser hastalarının bir kısmı, geleneksel kanser tedavilerini alırken, tamamlayıcı bitkisel tedavi kullanma eğilimindedir. Beta-glukanların bağışıklık sistemini uyarıcı etkisi yanında, kanser hücreleri üzerine doğrudan sitotoksik etkileri de vardır. Bu çalışmada, ekmek mayasından (Saccharomyces cerevisiae) elde edilen, 1,3-1,6 beta-glukan içeren besin takviyesi, sarkom tanılı hastalar tarafından kullanılmış ve retrospektif olarak beta-glukan kullanımının nötropenik ateş (NA) sıklığı ve sağkalım üzerine etkisinin değerlendirilmesi amaçlanmıştır.

Gereç ve Yöntem: 2014-2017 yılları arasında sarkom tanısı alan, beta-glukan kullanmış 27 hasta ve kontrol grubu olarak beta-glukan kullanmamış 31 hasta alındı. Hastaların klinik kayıtları geriye dönük olarak incelendi.

Bulgular: Beta-glukan grubunda NA geçiren hasta sayısı ve NA nedeniyle hastanede ortalama yatış süresi kontrol grubuna göre daha yüksekti ancak sonuçlar istatistiksel olarak anlamlı değildi. Genel sağkalım ve olaysız sağkalım açısından bakıldığında, beta-glukan ve kontrol grubunda 5. yılda genel sağkalım %83,3 ve %52,9, 5. yılda olaysız sağkalım %48,1 ve %71 idi.

Sonuç: Daha geniş hasta grubu ile prospektif olarak dizayn edilecek çalışmalar ile profilaktik beta-glukan kullanımının nötropenik ateş sıklığı ve sağ kalım oranları üzerine etkisi daha sağlıklı olarak değerlendirilebilir.

Anahtar kelimeler: Beta-glukan, nötropenik ateş, pediatrik sarkomlar, sağkalım

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INTRODUCTION

Some cancer patients tend to use complementary herbal therapy while receiving conventional cancer treatments such as surgery, chemotherapy, and radiotherapy.[1] Beta-glucans are a type of carbohydrates located in the cell walls of microorganisms, such as bacteria, fungi, yeast, cereal grains (oats and barley), and algae.[2] Beta-glucans are composed of glucose units linked by several different types of beta-glycosidic bonds, resulting in a linear or branched structure. There are several known configurations of beta-glucan bonds, including β(1,3), β(1,4), and β(1,6), but only molecules with a β(1,3)-bound D-glucose backbone showed immunomodulatory and stimulatory activity; therefore, these molecules have been classified as biological response modifiers (BRMs).[3]

In general, the immunostimulating effect of beta-glucans has been well studied, and numerous beta-glucan receptors have been identified on the surface of immune cells. In addition, it has been demonstrated that beta-glucans have direct cytotoxic effects on cancer cells; they have also been used in cancer therapy.[4]

Soft-tissue and bone sarcomas, such as rhabdomyosarcoma, synovial sarcoma, Ewing sarcoma, and osteosarcoma, are aggressive, high-grade malignancies that often occur in adolescents and young adults. They are treated with multimodal treatment options, including chemotherapy, radiotherapy and surgery.

Neutropenic fever (NF) is one of the most important acute side effects of chemotherapy for cancers affecting the pediatric age group. Delaying chemotherapy cycles because of the incidence of NF can reduce the effectiveness of treatment, causing serious morbidity and even mortality; therefore, it is important to minimize the incidence of this side effect of chemotherapy with supportive treatment.[5]

There are many studies in the literature confirming the therapeutic benefits of beta glucans in adult cancers. However, there is still a lack of information comparing the effects of such products on pediatric cancer patients and also patients with sarcoma. In this study, beta-glucan, which is obtained from baker's yeast (Saccharomyces cerevisiae) and used as a food supplement containing β(1,3)-β(1,6) beta-glucan, was used by patients diagnosed with sarcoma, and this study aimed to retrospectively evaluate the effect of beta-glucan use on the incidence of NF and survival rates in pediatric patients with sarcoma.

MATERIALS AND METHODS

Patients

Patients who were diagnosed with bone or soft-tissue sarcoma at the Pediatric Oncology Clinic of Çukurova University Hospital between 2014 and 2017 were included in this retrospective study. The data were obtained from pediatric oncology patient files and hospital computer records.

The following patients were excluded from this retrospective study: patients with missing data in their patient files, patients who went to another center after diagnosis or during the treatment process, patients who were diagnosed in an external center and presented for continuation of treatment after their treatment was initiated, and patients who were diagnosed with relapsed sarcoma in another center and presented for advanced treatment.

The ethics committee approval with the decision number 111/98 dated 21.05.2021 was obtained from Çukurova University Faculty of Medicine Clinical Research Ethics Committee. Verbal and written informed consents were received from the legal guardians of the patients and controls.

The food supplement named Imuneks®, containing 1,3-1,6 beta-glucan, obtained from baker's yeast (Saccharomyces cerevisiae), was a product frequently shown in television advertisements in Turkey between 2014-2017, available without a prescription from pharmacies, and popularly used among our cancer patients at that time. The use of this food supplement has increased, especially among sarcoma patients, as the physicians following the patients also suggested the use of this product. It was observed that the dosage of this food supplement used by the patients was according to the manifacturer's prescription.

Study procedures

Patients in the beta-glucan group comprised of patients who regularly used beta-glucan for one year in addition to the standard chemotherapy accepted as disease-specific after diagnosis. It was observed that patients up to 12 years of age used the syrup form containing pure beta-glucan at a dose of 20 mg/day, and patients aged ≥12 years used the capsule form

containing pure beta-glucan at a dose of 50 mg/day. Patients who were diagnosed with bone or soft-tissue sarcoma in our clinic between 2014 and 2017 and did not use beta-glucan were included in the control group.

The follow-up and evaluation of the use of this food supplement by the patients included in the study as the beta-glucan group was performed by a specialist doctor. A retrospective side-effect evaluation was also performed by this doctor.

Neutropenia was defined as cases in which the absolute neutrophil count was <500/mm^3 or the neutrophil count was 500–1000/mm^3 and was expected to fall <500/mm^3 within 48 hours. Fever was defined as a tympanic or skin temperature of ≥38.3°C at a single measurement or of 38.0°C that lasts for one hour.[6] Pediatric patients with sarcoma who were diagnosed with and were at a at high risk for NF were hospitalized and broad-spectrum antibiotics were empirically initiated. These treatments were revised according to the culture results and clinical conditions of the patients. NF was treated in accordance with the Infectious Diseases Society of America Clinical Practice Guidelines.[6]

Treatment procedures

The EURO-E.W.I.N.G. 99 based chemotherapy protocol was followed for the treatment of patients with Ewing sarcoma, EURAMOS-1 based chemotherapy protocol was followed for the management of patients with osteosarcoma, and Children's Oncology Group Soft-Tissue Sarcoma based chemotherapy treatment protocol was followed for the management of patients with rhabdomyosarcoma and other soft-tissue sarcomas[7-9]

File records of patients in the beta-glucan and control groups were examined, and overall survival (OS) rate, event-free survival (EFS) rate, incidence of NF during the treatment, the number and duration of hospitalizations, and the final condition of the patients were evaluated.

Statistical analysis

Statistical package for the social sciences 22 software package was used in the statistical analysis of the data obtained. Categorical variables (such as gender, presence of metastases, frequency of NF) were analyzed using the chi-square test, non-parametric variables (hospitalization duration of the two groups) were analyzed using the Mann–Whitney U test, and normally distributed numerical variables (mean ages of groups) were analyzed using the Student's t-test. Kaplan–Meier survival analysis was used to evaluate survival rates. A value of $P<0.05$ was considered statistically significant.

RESULTS

Between 2014 and 2017, 92 patients who were diagnosed with bone and soft tissue sarcoma were identified. The study included 27 patients with sarcoma who used beta-glucan in the beta-glucan group and 31 patients with sarcoma who did not use beta-glucan in the control group. The male/female ratio was 2 in the beta-glucan group, whereas it was 1.6 ($p=0.79$) in the control group. The mean ages of patients in the beta-glucan and control groups (10.78±4.17 and 10.26±5.11 years, respectively) were similar. The distribution of the diagnoses of all patients is provided in Table 1.

Table 1. Distribution of patients according to their diagnoses

	Beta-glucan group N	Control group N	Total N (%)
Ewing sarcoma	10	9	19 (32.7%)
Osteosarcoma	7	12	19 (32.7%)
Rhabdomyosarcoma	7	9	16 (27.7%)
Fibrosarcoma	0	1	1 (1.7%)
Malignant mesenchymal tumor	3	0	3 (5.2%)
Total N (%)	27 (46.6%)	31 (53.4%)	58 (100%)

Metastasis was detected at the time of diagnosis in 10 (37%) patients in the beta-glucan group and in 11 (35%) patients in the control group ($p=1$), and lung metastasis was found in 7 (25.9%) patients in the beta-glucan group and in 11 (35.5%) patients in the control group ($p=0.571$). Further, a relapse was detected during follow-up in 10 patients (37%) in the beta-glucan group and in 4 patients (12.9%) in the

control group. The presence of metastasis at diagnosis and relapse during follow-up were similar in both the groups (p=1.0, p=0.571 and p=0.063, respectively).

Data regarding the incidence of NF during the treatment process and the number and duration of their hospitalizations because of NF is provided in Table 2. The number of patients who had NF and the mean length of hospital stay because of NF were higher in the beta-glucan group than in the control group, but the results were not statistically significant (p=0.28 and p=0.391, respectively).

The OS rates at 5 years were 83.3% and 52.9% and EFS rates at 5 years were 48.1% and 71% in the beta-glucan and control groups, respectively (p=0.30 and p=0.12, respectively).

Table 2. The incidence of neutropenic fever

	Number of patients who had NF (%)	P	NF hospitalization (days) median (min-max)	P
Beta-glucan group (N=27)	19 (70.3%)		7 days (0-69)	
Control group (N=31)	17 (54.8%)	0.283	3 days (0-91)	0.391

NF: Neutropenic fever

DISCUSSION

The main treatment method that is used in combination with surgery and radiotherapy in the treatment of sarcomas is chemotherapy. Systemic chemotherapy administered to patients has the most profound effect on the rapidly proliferating bone marrow; the number of neutrophils decreases and their functions are suppressed. Thus, susceptibility to infections is increased. In addition, the gastrointestinal mucosa is seriously damaged, and the risk of invasive infection caused by microorganisms colonized in the intestinal mucosa increases.[10]

Complementary and integrative therapies (CITs) are commonly used worldwide by pediatric patients with cancer, and their use is influenced by geography and culture.[11] Most patients find CITs helpful and safe. The frequency of the use of CITs by pediatric patients with cancer is in the range of 6%–100%.[12] Dietary supplements, such as herbal medicines, vitamins, and minerals as well as other methods, such as dietary changes, massage, exercise, and worship, are commonly used around the world.[11] A positive and similar association has been reported between the use of CIT and lifestyle therapies, such as dietary changes and exercise, among pediatric cancer survivors.[13] Beta-glucans, which are dietary supplements, are often used by pediatric patients with cancer worldwide.

Many studies have attempted to demonstrate that beta-glucans act as BRMs in vitro and in vivo, stimulate the immune system, and ultimately aid in cancer remission.[14] In this regard, numerous animal experiments, which have shown the immunomodulatory and cytotoxic effects of beta-glucans, have been conducted. For example, a study conducted by Sonck et al. on pigs found that beta-glucans can stimulate the innate immune system, thereby improving defense against infections, as well as activating monocytes, macrophages, and natural killer cells.[15] On the other hand, Xiao et al. observed in their study that soluble beta-glucans caused an increase in the immunity of pigs by increasing the production of interferon gamma (INF-γ).[16]

A study regarding the use of beta-glucans as an adjunct in the treatment of patients with cancer reported that this agent can be administered orally, intramuscularly, or intravenously.[17] We preferred using its oral form, which is its most commonly used form in literature, because a study demonstrated that orally administered beta-glucans are absorbed from the proximal intestine via intestinal epithelial cells or M cells in Peyer's patches, and are then identified by dendritic cells (DCs) and macrophages in the GALT system.[3] Binding of beta-glucans to antigen presenting cells (APCs) causes these cells to migrate to the bone marrow or lymph nodes. In the bone marrow, beta-glucan degradation products bind to CR3 on the neutrophils, leading to their activation, whereas in the lymph nodes, activated APCs stimulate the production of effector lymphocytes by producing proinflammatory cytokines.[18] We believe that the beta-glucan product taken orally may be effective in the management of NF via this mechanism. In addition, only oral formulations are allowed as dietary supplements by the FDA (US Food and Drug Administration), EFSA, and the

Ministry of Agriculture, Food and Livestock in Turkey.

There are many clinical studies on the use of beta-glucan in patients with cancer. Karaca et al., in their study, administered 50 mg/day of pure beta-glucan orally to patients with colorectal cancer for 1 week. Leukocytes were counted before and after three cycles of chemotherapy in the beta-glucan group and in the control group that did not use beta-glucan. While the decrease in leukocyte count after chemotherapy was limited in the group that received beta-glucan, there was a significant decrease in the leukocyte count in the group that received chemotherapy alone. The results of the study showed that the use of oral beta-glucan reduces the side effects of chemotherapy, including diarrhea, neutropenia, and oral mucositis.[19] Further, oral beta-glucan was used in patients with advanced breast cancer in a study by Demir et al., and it was reported that oral beta-glucan stimulated the proliferation and activation of peripheral blood monocytes.[20] On the other hand, in our study, we found that the use of beta-glucan did not result in a significant difference in the incidence of NF and the length of hospital stay because of NF between the groups.

Contrary to our study, in a study conducted by Ostadrahimi et al. on breast cancer patients, 20 mg 1-3, 1-6 beta-glucan was orally administered in combination with chemotherapy to 15 breast cancer patients for 21 days, and it was found that there was a less decrease in the white blood cell counts of the patients using beta-glucan compared with that in the group comprising of patients who were not using beta-glucan on the 21st day.[21]

Beta-glucans have anti-carcinogenic properties as well as immunomodulatory effects. These anti-carcinogenic properties have been demonstrated in several studies in which purified beta-glucans were used. Beta-glucans have been used as adjuncts, especially in clinical studies conducted in the Far East, with positive effects on patients' survival and quality of life.[22]

In our study, no difference was observed between the beta-glucan and the control groups in terms of OS and EFS rates. Engel-Redel et al. used bevacizumab, carboplatin, and paclitaxel together with BTH1677 (Imprime PGG), a 1,3-1,6 beta-glucan obtained from the baker's yeast (Saccharomyces cerevisiae), in 59 patients with advanced non-small cell lung cancer, at an intravenous dose of 4 mg/kg once a week for 3 weeks and reported improvements in the response of the tumor to treatment and survival rate compared with the control group that was not given beta-glucan.[23]

Dietary supplements other than beta-glucan are also used among patients with cancer against cancer or to reduce the side effects of cancer treatment. A nutritional supplement named Avemar, which is a fermented wheat germ extract, has been used in pediatric patients with solid cancers, and the effect of this agent on the incidence of NF has been investigated. Twenty-two children with various types of solid cancer were included in the study. Avemar was administered to 11 children, and 11 children were included in the control group in the study. Avemar was shown to successfully reduce life-threatening NF attacks with its immune system stimulating and bone marrow protective effects.[24] Martinez et al., in their study, evaluated the efficacy and safety of oral magnesium supplements in reducing the incidence of NF in children with solid tumors treated with cisplatin-based chemotherapy, and showed that oral magnesium supplements reduced the incidence of NF in the experimental group compared with the control group.[25]

Muramyl tripeptide phosphatidyl-ethanolamine (MTP-PE), which can be used in addition to standard chemotherapy in patients with osteosarcoma, which acts as a non-specific immunomodulator by activating monocytes and macrophages involved in increased tumoricidal activity and secretion of proinflammatory cytokines.[26] MTP-PE was developed to help prevent lung metastasis in osteosarcoma.[27] Meyers et al. and the Pediatric Oncology Group reported that the addition of this agent to the treatment had a positive effect on OS and EFS rates, but the results of the study are controversial due to the simultaneous addition of ifosfamide to the treatment. Moreover, the cost of MTP-PE is very high and beta-glucan is a cost effective and safe dietary supplement without serious side effects.[26,28,29]

There is no study in the literature evaluating the use of beta-glucan in patients with sarcoma. Studies have been mostly carried out on adult patients with gastrointestinal, breast, prostate, lung, and ovarian cancers. In addition, there is no study conducted on pediatric patients with cancer. Therefore, our study, which evaluated the use of beta-glucan in patients with pediatric sarcoma, is different from the literature. However, there were some limitations in

our study. As our study was retrospective, data on beta-glucan use are based on patient statements. Another limitation of this study is the grouping of patients with different sarcoma diagnoses and different chemotherapy regimens.

The patients were also questioned in terms of side effects associated with the use of beta-glucan. No side effects that were considered to be associated with this product were reported by the patients who used beta-glucan.

In conlsuion, the use of beta-glucan in pediatric sarcoma patients did not affect the number of NA attacks and the length of hospital stay for NA. The beta-glucan group had a higher OS rate (83.3%) at 5 years, but these results were not statistically significant. The effect of prophylactic beta-glucan use on the incidence of NF and survival rates in pediatric patients with sarcoma should be evaluated more reliably in further prospective studies with a large patient group.

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