Significant prolongation of disease-free period gained by oral polysaccharide K (PSK) administration after curative surgical operation of colorectal cancer

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Summary. To examine the clinical efficacy and the mechanism of action of polysaccharide K (PSK), a protein-bound polysaccharide extracted from a Basidiomycetes fungus, a randomized double-blind trial was performed by administering PSK to 56 patients and a placebo to another group of 55 patients after surgical operations on their colorectal cancers. The rate of patients in remission (or disease-free) was significantly higher in the PSK group than in the placebo group; the difference between both groups was statistically significant at $P < 0.05$ by the log-rank test. The survival rate of patients was also significantly ($P < 0.05$) higher in the PSK group than in the control group. The most significant laboratory finding was that polymorphonuclear leukocytes from PSK-treated patients showed remarkable enhancement in their activities, such as random and/or chemotactic locomotion, and phagocytic activity, when compared with those in the control group. In conclusion, PSK was useful as a maintenance therapy for patients after their curative surgical operations for colorectal cancer. The beneficial effects were probably due to the activation of leukocyte functions as one of the many biological-response-modifying (activities induced by PSK).

Introduction

During the last decade or so, immunotherapy as one of the multidisciplinary treatments for advanced cancer has gained momentum in its rapid progress through the development of immunostimulators, which potentiate host defense mechanisms [17, 18, 21, 22, 33]. Among the many immunostimulators developed thus far, OK-432 (a streptococcal preparation) [8, 13, 28, 34, 36, 39] and polysaccharide K (PSK, a plant-derived polysaccharide) [5, 14, 24, 25, 32], have been used most often in Japan. PSK especially is an interesting drug because its oral administration induces the activation of the host immune system to show antitumor activity [1, 10, 27, 41].

For a long time in Japan it has been believed beneficial, though without solid evidence, that cancer patients orally take the boiled extract of polyporaceae species. Technical and theoretical progress in modern medicine has shed light on the old approach for this incurable illness. Thus, a partially purified protein-bound polysaccharide extracted from a fungus called Coriolus versicolor (strain 101) of Basidiomycetes has been shown to have immunomodulatory activities, and its clinical usefulness has been established in various clinical trials in the early 1970s, resulting in the approval of the Japanese Health and Welfare Department for its usage in the treatment of certain types of cancer.

There have been a number of reports that show the clinical usefulness of PSK when used in combination with other chemotherapeutic agents for treating patients with cancer in various organs such as the stomach [5, 14, 20, 24, 25], uterus [30] or lung [4]. For example, Ito et al. [5] have reported that a group of gastric cancer patients at stage III treated with mitomycin C and PSK showed a longer survival time than those treated with mitomycin C alone. However, there have been few reports available that study the clinical effect of PSK alone on any type of cancer, especially colorectal cancer, as will be described in this paper. Although PSK has been shown to have various immunostimulating activities in vivo as well as in vitro, the exact mechanism of its action has not been well understood. Therefore, an attempt was also made to analyze the underlying mechanisms of the anti-cancer activity of PSK in this study.

Materials and methods

PSK. A boiled aqueous extract of the cultured mycelia of Coriolus versicolor, a Basidiomycetes fungus (Fig. 1), was precipitated by ammonium sulfate and the desalted powder was designated as PSK (protein-bound polysaccharide Krhe, (reviewed in [35]). This compound con-
contains about 15% protein and its average relative molecular mass is approximately 100,000. The sugar portion consists of five kinds of sugar, mainly glucose, and a major protein has a straight-chain structure with \((\beta-1-4)\)-glucan branching at the 6 or 3 position. The protein consists of 19 amino acids, mainly aspartic acid, glutamic acid, and leucine. Because Sephadex G-100 gel filtration shows multiple peaks, naturally PSK is not represented as a single entity rather as a mixture of substances. Since PSK is a brown tasteless powder easily soluble in water, the placebo in the present trial was also made as a brown powder (Fig. 1d and Fig. 1e). Each batch of PSK is produced in a modern pharmaceutical factory under a highly quality-controlled system. The reproducibility of different batches is always assured by an assay in which the antitumor effect of a tested batch on experimental tumors in vivo (sarcoma 180) in ICR mice is equivalent to that of an internal standard.

Patients. The anti-cancer effect of PSK was evaluated in patients with advanced colorectal cancer in a randomized double-blind trial. The placebo for PSK (PSK-P) was a brown powder resembling PSK, composed of mannitol and caramel, 79% and 21% respectively. Either PSK or a placebo was randomly administered to a total of 120 patients. A total of 61 patients were entered in the PSK group; 5 died of causes unrelated to cancer (myocardial infarction, diabetes, hypertension, traffic accident, and cerebral infarction), 2 went to other hospitals to be treated with anti-cancer chemotherapy and 5 took PSK only for the first 2 weeks and never came back to the clinic; they were, therefore dropped from the final analysis, leaving 56 patients for evaluation. Among the 59 patients entered in the PSK-P group, 6 patients died of causes unrelated to cancer (cerebral hemorrhage, myocardial infarction, traffic accident, cerebral infarction, and acute heart failure) and 4 patients took PSK-P only for the first 2 weeks and never came back to hospital again. Thus, 55 patients were evaluated in the placebo group. As shown in Table 1, these two groups of patients were almost equivalent in terms of age, surgical operative methods employed, histological diagnosis, and cancer stages, which were established by Japanese Research Society for Cancer of the Colon and Rectum [7]. Stages III and IV of the macroscopical classification of colorectal cancer corresponded to Dukes C (Dukes' classification). The microscopical cancer stage was determined by a single pathologist. Other factors, such as choice of anesthetics, duration of anesthesia and operation, number and amount of blood transfusions, etc. were not significantly different between both groups.

Administration schedule of PSK and placebo. The first administration of PSK or placebo (PSK-P) started 10–15 days after surgical operations. A dose of 3 g was taken orally daily until 2 months after surgery, then 2 g daily until 24 months and 1 g daily thereafter. When distant metastasis or recurrence was detected in any patient during the follow-up period after surgery, the patient was immediately removed from this oral drug administration protocol and was put under a new treatment protocol including reoperation and immunochemotherapy, which was determined to be the best for that patient at that time. This protocol was adapted from a similar one employed in our previous trial of PSK on gastric cancer [11].

Skin tests. Before and 2 months after the surgery, skin reactivity was tested with various antigens and mitogens such as phytohemagglutinin protein (PHA-P), p-phenylenediamine (PPD), dinitrochlorobenzene (DNCB) and keyhole limpet hemocyanin (KLH).

Circulating T lymphocytes and responsiveness to PHA. T and B lymphocytes in peripheral blood were counted using a modification of Tachibana and Ishikawa's method [31]. The normal ranges of T and B lymphocytes in 50 healthy volunteers were 64.5 ± 9.8% and 35.1 ± 8.9% respectively. Blood mononuclear cells were stimulated with PHA-P and its stimulation index was determined as described previously [33].

Serum sampling. Approximately 10 ml blood was obtained aseptically by venipuncture. Blood was left to clot at room temperature for 1 h and serum was separated by centrifugation at 800 g for 10 min and stored at −70 °C until use.