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A Turkey Tails Polysaccharide as an Immunochemotherapy Agent in Cancer

Kathy Abascal, B.S., J.D., R.H. (AHG), and Eric Yarnell, N.D., R.H. (AHG)

Abstract

Trametes versicolor or *Coriolus versicolor* (turkey tails) is a medicinal mushroom containing a number of protein-bound polysaccharides that have shown strong potential in the treatment of cancer. This discussion examines the use of Polysaccharide Krestin (PSK), a proprietary polysaccharide extracted from *T. versicolor*, in the treatment of gastric, colorectal, lung, breast, and esophageal cancers. PSK has been approved in Japan for use as an adjunct to surgery, chemotherapy, and radiation therapy for cancer, and has shown significant benefits. This agent appears to act in part by restoring the balance of dendritic and T-helper cells and cytokines related to these cells' function and maturation in cancer patients.

Introduction

The fan-shaped mushroom known as turkey tails (*Trametes versicolor* or *Coriolus versicolor*) can be found growing on logs throughout the United States, Europe, and Asia. It has a distinctive cap that is "zoned" into bands of brown, white, gray, or blue, and grows in overlapping clusters. Turkey tails does not have a culinary use, but it is said to make a pleasant, mushroom-flavored chewing gum. And although it was recognized as a medicinal agent in the Chinese materia medica thousands of years ago,[1] turkey tails is not a mushroom that has a central place in traditional medicine, like *Ganoderma lucidum* (reishi), *Cordyceps sinensis* (cordyceps), or *Lentinula edodes* (shiitake). Nonetheless, a proteoglycan from turkey tails is today used in treating cancer in Japan. Surprisingly, the potential benefits of turkey tails are largely ignored by mainstream oncology in North America.

Polysaccharides

Mushroom proteoglycans consist of protein-bound polysaccharides, and are recognized as having anticancer potential. This presentation reviews the use of a turkey tails proteoglycan, (Polysaccharide Krestin), in treating cancer. PSK, sometimes referred to by the brand name Krestin under which it is available on a proprietary basis, has been used in Asia in treatment regimens for cancer for over 30 years. This agent was reportedly discovered when a Japanese engineer observed a neighbor with a life-threatening cancer go into remission after taking turkey tails mushrooms.

PSK is water-extracted from a particular strain of turkey tails (CM-101) and is orally bioavailable.[2] It is nontoxic and has shown a high degree of safety in chronic and subacute toxicity studies. The only significant side effect of PSK observed in clinical practice is reported to be an occasional darkening of the fingernails.[2]

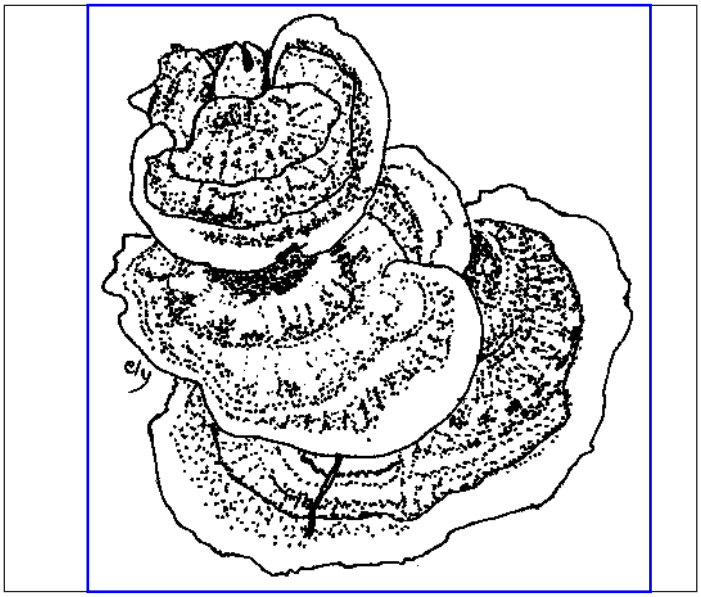
In Japan, PSK is typically used as an adjunct to conventional cancer treatments, and has only rarely been studied by itself in treating cancer. However, a placebo-controlled, double-blind trial involving 144 patients with stage III gastric cancer found that PSK significantly extended disease-free survival, although it did not strikingly extend overall survival.[3] The patients were given PSK in a dose of 3 g daily for up to 2 months, 2 g daily for the next 2–14 months, and 1 g daily from 14 to more than 80 months after surgical resection, to the endpoints of disease recurrence or distant metastasis. The study found that PSK increased immunocompetence and appeared to require some degree of residual immune function for positive effects.[3]

In a subsequent study of 111 patients with stages III and IV colorectal cancer, treated with the same protocol as in the study just described, PSK improved 8-year survival to 40% versus 25%, and disease-free survival to 25% versus 8% as compared to placebo.[4]

PSK as an Adjunctive Agent

Since the 1970s, numerous clinical trials have investigated PSK as an adjunct to chemotherapy for cancer. These studies suggest that PSK is most strongly indicated for cancers of the stomach, esophagus, colon, rectum, and lung.

At least 10 studies have examined PSK as a component of long-term chemotherapy for resected stomach cancer.[2] In all of these studies PSK was administered orally at a dose of 3 g/day. In one of the earliest studies, a group of 66 patients with stage IV stomach cancer were treated with mitomycin-C



Trametes versicolor **(turkey tails). Drawing ©2007 by Eric Yarnell, N.D., R.H. (AHG).**

beginning on the day of surgery, followed by long-term immunochemotherapy with a 5-fluorouracil (5-FU) derivative plus PSK, with periodic administration of mitomycin-C. The 2-year survival for this group was more than twice that of a similar group of patients treated with surgery and mitomycin-C but without 5-FU or PSK.[5]

Subsequent studies using a similar regimen also had positive results. In a study of 110 patients with stomach cancer of all stages, the postoperative combination of mitomycin-C with long-term administration of tegafur (F-207) and PSK improved 3-year survival, and no deaths were reported for the first 2 years after surgery in a subset of patients with stage III disease.[6]

In 450 patients with advanced stomach cancer and invasive metastasis, the combination of mitomycin-C given after resection, with long-term tegafur/PSK, doubled the rate of 5-year survival over the chemotherapy regimen alone.[7] In two further studies, of 579 patients with invasive metastasis and 53 patients with stage III stomach cancer, respectively, PSK again increased the rate of 5-year survival.[8,9] Other studies had similar findings for 5-year survival, and in one, PSK extended 15-year survival.[10–12]

Current Status of PSK in Gastric Cancer

In Japan, PSK dosed at 3 g/day is approved as part of the standard treatment regimen for gastric cancer, and is covered by insurance. Currently, the view is that the overall effect of PSK is enhanced by alternating periods of its use with periods of chemotherapy.[13] Other studies of patients most helped by PSK suggest that it is highly likely to increase long-term survival in patients with limited dendritic-cell infiltration of gastric tumors at the time of surgery.[9]

PSK and Metastasis

Metastasis is the ultimate cause of death in the vast majority of patients who have cancer. Metastasis is a cascade of events beginning with the escape of cancer cells from a primary tumor and ending in the growth of these cells into new lesions at sites other than that of the primary tumor. Intervention at any point in this cascade of events is beneficial in combating cancer, and PSK shows potential at many points in this process.

In a study in which mice were inoculated in both flanks with fibrosarcoma cells, the injection of PSK into one of the resulting tumors enhanced the activity of cytotoxic macrophages, causing this metastatic tumor to shrink. Orally administered PSK also decreased the number of metastatic nodules in this animal model of spontaneous metastasis, and showed an ability to inhibit both the intravasation of cancer cells from the primary tumor into the circulatory system and the extravasation of tumor cells from the circulation to new sites of tumor growth.[a]

[a]Ref. 18.

Colorectal Cancer

With establishment of the benefits of PSK as an adjunct to chemotherapy for gastric cancer, investigations began of the agent's potential benefits in colorectal cancer. In a large multicenter trial, 448 patients treated surgically for colon or rectal cancer were randomized to receive either chemotherapy alone or PSK plus chemotherapy. After the third year of treatment, PSK had significantly improved both survival and the disease-free interval in the colon-cancer group but not in the group with rectal cancer.[14]

In a comparative study in which patients with untreated stage II or III colorectal cancer underwent surgical resection and were given a fluoropyrimidine after surgery, the 3-year disease-free survival rate was 74.3% for PSK plus chemotherapy, as opposed to 40.0% for chemotherapy alone.[15] A marker of hepatic metastasis in gastrointestinal (GI) cancers, type IV collagen, was present at significantly lower levels in the blood of patients given PSK plus chemotherapy than in the chemotherapy-only group for the first 12 months after surgery.[15]

In a multicenter study of metastatic colon cancer with a 7-year follow-up, PSK was given in alternating cycles with 5-FU for 10 courses while a second cohort of patients received only 5-FU.[13] The mortality rate in the PSK-plus-5-FU-treated group was 16.8%, versus 22.1% with 5-FU alone.[13] While disease-free survival was similar for the two study groups, 7-year survival was significantly greater in the PSK group than in the chemotherapy-only group, at 83.4% versus 78.5%. No toxic effects of PSK were found in a meticulous review of the patients' medical records.

The 5-year follow-up of a randomized, controlled, 2-year comparison of chemotherapy with tegafur plus 5-FU showed a significant benefit from the addition of PSK in stage II and III colorectal cancers.[16] The mean disease-free survival in the tegafur/5-FU/PSK group was 50.3 months, versus 40.0 months in the group given chemotherapy alone; 5-year disease-free survival was 73.0% in the former group versus

58.8% in the latter. The addition of PSK reduced disease recurrence by 43.6% and mortality by 40.2%.[16] PSK significantly increased disease-free and overall survival in cases of stage III disease (60.0% and 74.6%, versus 32.1% and 46.4%, respectively).

A recent meta-analysis found that adding PSK to the treatment of colorectal cancer (n = 1094) significantly improved overall and disease-free survival as compared to chemotherapy alone.[17]

PSK and Other Cancers

Two studies have looked at PSK in esophageal cancer. One of these was a retrospective, noncontrolled study of 133 patients to whom PSK was given after surgery and radiation therapy. The researchers concluded that PSK significantly improved 1- and 2-year survival.[18] In a prospective, randomized study of 158 patients, PSK, again given after surgery and radiation therapy, significantly improved the 5-year survival rate as compared with surgery and radiation alone.[19] This study found that PSK improved survival in patients with abnormally high levels of alpha-1-antichymotrypsin, sialic acid, or both.[19]

Adding PSK to the treatment of colorectal cancer significantly improved overall and disease-free survival as compared to chemotherapy alone.

In a study of 34 patients with nasopharyngeal cancer who had undergone radiation and various forms of chemotherapy before being randomized to receive PSK or placebo, the patients given PSK had a 5-year survival rate of 28%, versus 15% for the placebo group.[20] When given after radiation therapy in 2-week cycles to 185 patients with non–small-cell lung cancer, PSK was associated with a 5-year survival of 27%, versus 7% for placebo. Patients with stage III disease fared better than those with stage I or II disease.[21]

The benefit of PSK in breast cancer is more varied than that in GI cancer. A retrospective analysis of breast cancer patients treated for recurrent disease with surgery followed either by mitomycin-C alone or by mitomycin-C plus PSK found that the latter regimen significantly extended survival over surgery or surgery plus mitomycin-C.[22] A study of patients with vascularly invasive breast cancer found strong trends toward extended 10-year survival with PSK given together with chemotherapy after surgery, as opposed to surgery and chemotherapy alone, and also found extended disease-free intervals, but lacked statistical evaluations.[23,24] A retrospective analysis of PSK in breast cancer showed that patients with HLA B40+ type breast cancers who received PSK had a 100% survival at 10 years, even though the use of PSK has not shown a clear benefit in breast cancer treatment overall.[24]

A multicenter study of 67 patients in remission following initial chemotherapy for acute nonlymphocytic leukemia, who were randomized to receive 2 years of maintenance chemotherapy with or without PSK given for as long as 4.5 years, found a trend toward benefit from the addition of PSK.[25]

How Turkey Tails Affects the Immune System

PSK is used to support and stimulate the immune system in cancer and to offset the immunosuppressive effects of allopathic cancer treatments. Research is being conducted to explain the many ways in which PSK acts to produce these effects. One of the most interesting areas of such investigation seeks to determine how PSK affects dendritic and T-helper cells and the cytokines they secrete.

In the normal function of the immune system, antigen-presenting cells, such as dendritic cells, activate T-helper (Th) cells.[3] Once activated, Th cells coordinate the response of other immune cells. The balance between two types of Th cells—Th1 (Type 1) and Th2 (Type 2) cells—is of great importance in cancer.

The substances secreted by Th1 and Th2 cells to maintain their normal balance are known as cytokines and chemokines. Immune cells function through a complex interplay of such substances. The body uses the cytokine interleukin-12 (IL-12) as one of its tools to defend against tumors. This cytokine helps Th1 cells to proliferate, activate, and mature. IL-12 also augments natural-killer (NK) cell cytotoxicity against tumor cells. However, when the body is in a cancer-bearing state, IL-12 production tends to be suppressed, which decreases Th1 activity. Th2 dominance increases the production of a different cytokine, IL-10, and when IL-10 is strongly expressed, dendritic cells produce virtually no IL-12 and are unable to induce the activation and maturation of Th cells.[3]

In healthy individuals, Th1 cells mobilize a defense against cancer cells. But if they evade detection and grow, cancer cells secrete substances that create a Th2 dominance, making the host less able to challenge them.[3] Studies indicate that cancer significantly reduces Th1/Th2 and dendritic cell type (DC1/DC2) ratios, causing an inefficient immune response to the disease.[6] Surgery causes a brief period of Th2 dominance that may give residual tumor cells an opportunity to evade the immune system.[5] Other causes of Th2 dominance include exposure to heavy metals.[4] PSK, and some other plant polysaccharides, help the body shift back to Th1 dominance, which leads to a more effective response to cancer.

In a small study of patients with gastric and colorectal cancer, treatment with PSK shifted the Th1/Th2 and DC1/DC2 balances to favor Th1 and DC1 dominance, respectively, significantly decreasing IL-10 production.[6] Other studies confirm the ability of PSK to promote Th1 dominance.[7,8] In patients with colorectal cancer, PSK decreased amounts of Th2 cytokines in responders but not in nonresponding patients, and strongly reduced IL-10 production in another study of patients with advanced cancer.[7,8]

In patients with highly advanced cancer treated with PSK and chemotherapy, the production of IL-10 and other Th1-suppressing factors decreased significantly.[9] In vitro, PSK was found to

PSP, Another Turkey Tails Proteoglycan

In China, the turkey tails proteoglycan, PSP, is used in treating cancer.[a] In patients with stomach, esophageal, and non–small-cell lung cancers, PSP has been reported to ease symptoms of radiation or chemotherapy and to enhance various immunologic functional parameters.[a]

It appears that PSP primarily ameliorates fatigue, loss of appetite, vomiting, dryness of the mouth, and other factors related to quality of life, but there is less evidence of PSP having direct effect on overall survival. However, one open-label, randomized trial in esophageal cancer found that PSP significantly improved both 1- and 3-year survival, and a subsequent study produced similar results.[b] Unfortunately, no studies have been reported on whether a combination of PSP and PSK might prove more useful than either compound used alone.

[a]Ref. 2.

[b]Ng TB. A review of research on the protein-bound polysaccharide (Polysaccharopeptide, PSP) from the mushroom *Coriolus versicolor* (Basidiomycetes: Polyporaceae). Gen Pharmacol 1998;30:1–4.

increase the maturation of dendritic cells.[26] This is noteworthy because immune depression in malignancy is associated with a failure of dendritic cell maturation.[6] In mice, PSK suppressed the increase in Th2 cytokines caused by surgery and prevented liver metastases of colon cancer cells injected into the spleen during surgery.[10] A study of rats found that preoperative administration of PSK prevented a decrease in postoperative cellular immunity.[11] Other studies found that PSK induced the Th1 cytokine IL-12. Taken together, these studies explain how the effect of PSK on the immune system improves the outcome of conventional cancer treatments that by themselves tend to depress the host immune response.

Conclusion

There is strong evidence that, when used as an adjunct to conventional cancer treatments, PSK can provide substantial benefit by restoring immune function, alleviating symptoms, and increasing survival. In view of this, it is confounding that so little clinical research has been done in the United States on PSK and similar proteoglycans.[27] PSK is not even readily available in the United States, although products that manufacturers claim are similar or identical to PSK are available under other names, such as VPS (MushroomScience, Eugene, OR).[28] Nor is information readily available on the quantity of PSK contained in the intact turkey tails mushroom, making it difficult to calculate an effective dose of PSK with use of the whole mushroom.

What is perhaps even more surprising is that so little basic research has been done on turkey tails itself. Research on PSK began with the observation that use of the whole turkey tails mushroom brought complete remission in a case of advanced cancer. However, other turkey tails' polysaccharides also show benefit in cancer (see box entitled PSP, Another Turkey Tails Proteoglycan). Research on the use of PSK combined with the turkey tails polysaccharide PSP, or on use of the whole mushroom, is definitely warranted to determine whether this may yield stronger beneficial effects than those already observed.[5] In any case, there seems no doubt that more practitioners should be advising patients on how PSK is used in Japan to improve outcomes with conventional cancer treatments. □

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Kathy Abascal, B.S., J.D., R.H. (AHG), is executive director of the Botanical Medicine Academy, Vashon, Washington. **Eric Yarnell, N.D., R.H. (AHG),** is president of the Botanical Medicine Academy, a specialty board for using medicinal herbs, and is a faculty member at Bastyr University, Kenmore, Washington.

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