The Use of Mushroom Preparations in Malignancies

Mushroom preparations are used widely in Asia as complements to conventional cancer therapies, and have been used so for many years. In the last ten years they have become more widely available in the western world. Various medications derived from different mushrooms, especially Coriolus, Shitake, Reishi and Maitake mushrooms, have been studied. Two other combination agents, active hexose correlated compound (AHCC), and MGN-3 deserve mention, particularly because of their widespread use.

Physiological Effects

Mushrooms are commonly thought of as immunopotentiating agents. Their effects, however, extend far wider than only the immunological system.

Their effects on the immune system are thought to be mediated through B-D glucan linkages in their chemical structure. These are monosaccharide polymers. These monosaccharides can also be linked to proteins, where they are then termed proteoglycans. Numerous immunologically related activites have been confirmed with the use of mushroom preparations, including dendritic cell maturation and activation, macrophage and phagocytic activation, NK cell activation, improvement of the CD4/CD8 and Th1/Th2 ratios, and increased production of various cytokines, including interleukins 1, 2, 6, 8, interferons and tumor necrosis factor (1,2,3). These could all be beneficial in patients with malignancies

In addition to their direct immune effects, mushroom preparations have been shown to have other effects that could be clinically beneficial for cancer patients. These include inhibiting important transcription factors that are antiapoptotic, such as NFkB, AP-1, and urokinase plasminogen activator (4,5,6). Mushroom preparations have been shown to have antioxidant properties, have been able to mimic the free scavenging effects of superoxide dismutase and can increase glutathione peroxidase activity (7,8,9). Other activites include the decreasing of myelosuppression associated with chemotherapy in a murine model, increasing hematopoesis (10), and the overcoming of resistance of tumor cells to complement mediated cytotoxicity (11). Monoclonal antibodies work through various mechanisms, including having direct tumor cytotoxic effects, through the activation and enabling of NK cells, and through complement mediated cytotoxicity. Studies have suggested that the combination of a B-glucan substance, such as found in mushrooms, can enhance the effect of monoclonal antibodies . Cheung has studied the effect of combining B-glucans with monoclonal antibodies in numerous tumor cell lines and has found a very significant enhancement of cytotoxicity (12,13). This appears to occur by overcoming tumor cell resistance to opsonization with the C3. With the burgeoning interest and increasing use of monoclonal antibodies, this property of mushrooms has potential importance.

Mushroom preparations, in addition to being investigated in cell culture, in vitro and animal studies, have been relatively widely studied in humans (compared to other integrative treatment modalities), including randomized clinical studies, with promising results. This is true especially for the preparations from *Coriolus* mushrooms, known as PSK or Krestin, and PSP. Most of the following discussion will be centered on these medications.

Clinical Trials with *Coriolus* Preparations

Medicines derived from the *Coriolus Versicolor* mushroom have been studied in patients with colorectal malignancies. Ohwada studied patients with Stage II or III colorectal cancer, comparing a group treated with surgery and chemotherapy versus a group which also received PSK produced from *Coriolus*. After three years they found a mild benefit in disease free survival (80.6 vs 68.7 p=0.02), and overall survival (87.3 vs 80.6 p= 0.024) in the PSK group. In stage III patients the three-year overall survival was improved (83 vs 59.3 p= 0.02). The treatment group also showed a decrease in distant metastases (0.05), particularly to the lung (0.01). (14)

Ito studied patients with Dukes C colorectal tumors, comparing 440 patients treated with either 5 FU and PSK, or with 5 FU alone. He found a statistical difference in cancer related deaths (49 vs. 37, p= 0.19) in the treated group (15).Other studies (16, 17) have supported these positive findings.

PSK has been extensively studied in gastric cancer, which is a very common malignancy in Asian countries. Kaibara compared a group with stage IV gastric cancer, comparing conventional chemo and surgical treatment with or without PSK. Two year survival was improved (34 vs. 15% p<0.05)(18). Numerous studies by the group of Kodama, Kano et al. confirmed significant benefit from the addition of PSK to the usual treatment regimens (19,20). A study by Nakazoto, published in the Lancet, showed a slight benefit in 5 year disease free and survival rate (70.7 vs. 59.4% p=0.047, 73 vs. 60% p=0.044), in the group treated with standard treatment and PSK versus the group without PSK(21).

Ogoshi compared patients with esophageal cancer treated with conventional treatment with or without chemotherapy, and found a non-statistically significant trend towards improvement in 5-year survival. They found that the improved survival was noted especially in patients with the presence of high levels of immunosuppressive substances sialic acid and alpha i-antichymotrypsin (22,23).

Hayakawa compared patients with non-small cell lung cancer who were treated with radiation therapy with or without PSK. Five year survival rates were significantly improved in the PSK group in stages I, II and III (39 vs 17, 26 vs 8%)(24).

Studies have also been reported in breast cancer and leukemias (see ref 1 for summary).

Studies with Other Mushroom Preparations

While the bulk of research has been with Coriolus derived medications, some provocative studies have looked at AHCC and MGN-3. MGN-3, which is a rice bran compound that is modified by mushroom enzymes, has shown very impressive results regarding augmentation of NK activity. Most of the studies have been done by a single group, so caution should be applied in the reproducibility of this data. The compound AHCC has been studied in numerous situations. A study in patients with hepatocellular carcinoma showed significant benefit when AHCC was employed after surgical resection (25). AHCC has been combined with genistein in a product called Genistein Combined Polysaccharide

(GCP). The presence of the isoflavone genistein might be helpful in patients with prostate cancer, both because of its estrogen like effects, as well as effects on protein kinase C. A provocative case report discussed the use of this product in a patient with prostate cancer. This patient had biopsy proven prostate cancer with a PSA of 19.7. He was treated for six weeks with GCP prior to radical prostatectomy. The PSA decreased to 4.2 and the surgical specimen showed no evidence of tumor (26).

Other mushroom preparations are of interest and have been studied in preliminary ways. *Maitake* mushrooms, particularly the D fraction, have been studied in animals and in vitro (27,28), showing results on relevant aspects of the immune system. Kodama used *Maitake* preparations, without chemotherapy, in patients with Stage IV tumors in different sites (lung, liver, breast), and found both laboratory and clinical evidence of improvement, including some patients with radiological evidence of tumor shrinkage and regression (29). Sliva (30,31) has performed a series of interesting experiments with *Reishi* mushrooms, showing beneficial effects on transcription factors as well as inhibiting migration of highly invasive prostate and breast cancer cells.

When patients are administered chemotherapy, common effects include immunosuppression, as well as an augmented production of transcription factors, such as NFkB and AP-1, which stimulate tumor growth and chemoresistance by various mechanisms. As noted above, mushroom preparations can potentially alleviate the immunosuppression, myelosuppression and transcription factor production that occurs in patients undergoing chemotherapy. Therefore their use alongside conventional chemotherapy can be expected to be beneficial. This appears to be confirmed in the numerous studies cited above.

Conclusions

In summary, mushroom preparations have been shown to have a wide range of physiological effects which are likely to be beneficial in patients with malignancies. These extend beyond immune system stimulation to additional effects on transcription factors, antioxidant effects, and inhibiting invasion. There are also intriguing studies combining their use with monoclonal antibodies. Clinical studies in a diverse range of tumors have shown mild to moderate additive benefits when combined with conventional treatment regimens. Although these preparations have been shown to have antioxidant effects alongside their other actions, no evidence for interference with chemotherapy or radiation therapy exists. Indeed the studies suggest the opposite; an augmentation of their benefit.

Numerous mushroom preparations are available, including combinations of different mushrooms, and products containing isolated B-glucans. The most widely studied mushrooms are those prepared from *Coriolus Versicolor*, where in addition to cell line, animal, in vitro and in vivo studies, numerous randomized clinical studies have been completed. Other mushrooms, especially *Maitake* and *Reishi*, have a more limited evidence base. Two unusual products, AHCC and MGN-3 are used and marketed widely, but have an interesting, but clearly smaller evidence base. Some products contain combinations of different mushrooms. Individual mushrooms have overlapping, but unique compositions and properties. These combination products might show synergistic actions, but have not been studied. The side effect profile of these preparations is minimal. Costs at the present time are not, however, insubstantial. A one-month course can cost between $100-200.

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