Clinical Implications of PSP in Oncology

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Abstract

Up to now, the three main weapons against cancer have been surgery, radiotherapy and chemotherapy. Although these classical methods of treatment have given fairly good results in general, the results have yet to be improved, especially in late cases. Thus for many years, the search for a more effective means of anti-cancer treatment has been going on world-wide. An ideal drug would of course be one that could directly kill all the cancer cells without harming the normal tissues, and also without causing general toxicity. However, at present a more practical approach is to use drugs that would either enhance the biological effects of radiation or of cytotoxic agents, or strengthen the organism's immunological defenses. In recent years, several such drugs have been undergoing clinical trials, for example, Misonidazole, RS 2508, OK-432, PSK, etc.

The drug that we shall talk about today is polysaccharide peptide, hereafter referred to as PSP. This is a polysaccharide isolated from Coriolus versicolor by Professor Qing-yao Yang. It is similar in many ways to Krestin (PSK) discovered by the Japanese scientists in 1965. However, laboratory data, as well as both in vitro and in vivo experiments have shown that PSP is more active than PSK. Nevertheless, as a clinical oncologist, I must emphasize that any anti-cancer agent, no matter if the action is direct or indirect, must all undergo clinical trials to prove their value. It is well known that many drugs have been found to be very effective at the experimental level in animals, but when applied to human beings, due to unacceptable toxicity at effective doses, there was only limited practical value. Such examples are quite abundant in oncology: the radiosensitizer Misonidazole is a recent one. In the laboratory, an enhancement ratio of 1.7 of radiation effects was found in mice, but when used in patients, an E.R. of 1.2 could be barely achieved due to toxicity, and even then the late reactions of neurotoxicity made the drug unacceptable for clinical use. The presently widely used cancer chemtoherapy drugs such as Adriamycin and Cis-platinum have similar problems that limit their effectiveness.

Just as with PSK, basic investigations of PSP regarding toxicities and pharmacological activities have shown that by oral administration, no disturbances of peripheral blood picture, bone marrow, gastrointestinal tract, liver and kidney functions have been found so far. Marked effect has been demonstrated in animal experimental tumors.

In the Cancer Hospital of the Shanghai Medical University, Dr. Xue et al have treated 151 cases of various kinds of cancer, such as esophagus, lung, mediastinum, etc. First of all, two very important clinical aspects of PSP have been shown in the course of treatment of these cases. No drug toxicity has appeared clinically, and there has been noticeable, sometimes remarkable anti-cancer effect. These effects have been confirmed by many other colleagues who have used PSP on their patients. Such a combination is ideal for further clinical investigation, without the hazards associated in clinical trials with other agents.

There are several paths of clinical investigation that should be considered.

1. The use of PSP as the main therapeutical agent, especially in late cases of cancer. The experience in Shanghai has shown that PSP may be unexpectedly effective in apparently hopeless cases, as evidenced by the results obtained for Ming Wei Fang, Fu Luncai, etc.

   In our Department of Radiation Oncology, we have treated 4 cases of lung carcinoma with PSP, and found that growth of tumor, as shown by consecutive X-ray films, was stabilized as compared to 5 other cases without PSP treatment.

2. The use of PSP in combination with radiotherapy. In the literature of Krestin, it was found that it increased the effectiveness of radiation on the Sarcoma 180 in mice. We thought that it might be the same in human patients. It is well known that whenever a drug is used in combination with other agents such as radiation or cytotoxic agents, there is always the question as to how it will interact with them, whether the effects will be additive or synergistic, and most important of all, whether there will be a gain in therapeutic ratio. A gain in therapeutic ratio means that the effect on cancer tissue is markedly more than that on normal tissue. The contrary would make the drug useless for clinical purposes. Due to the almost non-existent toxicity of PSP, we decided the use of PSP at least would not interfere with the radiation treatment. 41 cases of esophageal carcinoma were treated with a combination of PSP and radiation. The results have been very encouraging, as shown by the paper on these cases reported by Xue et al.

3. The use of PSP in combination with chemotherapy. The experience with PSK in experimental chemotherapy has shown that PSK was able to enhance the effects of the chemotherapeutic agents. Naturally, PSP would have probably an even better effect theroetically, but clinical trials are needed to see if the toxic effects of the classical anti-cancer drugs can be decreased while enhancing their therapeutic effectiveness on the cancer cells in human beings.
4. The use of PSP as a therapy adjvant to other methods of cancer treatment. As is well known, radiation and chemotherapy both affect the leucocytes markedly, as well as the general condition of the patients. Quite often, radiotherapy or chemotherapy has had to be interrupted or discontinued due to such reactions.

   Very encouragingly, PSP has been shown to be of notable value in this respect. The experience of the Changzhou Municipal Hospital of Chinese Medicine has shown that PSP is effective in maintaining or even raising the WBC in 6 cases of advanced cancer treated by chemotherapy. The WBC had dropped to below 4000. PSP was able to raise them all to above 4000, in one case even to above 7000. In all the cases, the general condition was improved when PSP was given.

   In our own cases, the value of PSP as an ajuvant treatment is quite evident, as Table 1 shows.

Table 1 Adjuvant effects of PSP

Symptoms	No. of cases	Positive Effects	%
Relief of pain	44	37	84
Improvement of appetite	39	35	89
Less radiation reaction	5	4	80

   However, it should be noted that relief of pain was most effective in cases with moderate pain. Acute severe pain still required stronger analgesics. Like other analgesics, the pain-relieving effect of PSP seemed to decrease with prolonged use.

5. The use of PSP as an immuno-potentiating agent. In oncology, it is well known that with our present methods of treatment, whether it be surgery, radiotherapy or

chemotherapy, one can never be sure that the "last cancer cell" has been eradicated. Ultra-radical surgery may still leave behind some cancer cells outside the surgical field, radical radiotherapy is limited in dosage due to damage to normal tissues, and really effective high dose chemotherapy is not possible due to general toxicity. Finally, there is always the shadow of distant occult metastasis existing already at the start of any treatment. Work in cancer immunology has shown that the human body can cope with a tumor containing 10^5 cancer cells when the immunological defenses are in an active state. This state is impaired in patients suffering from cancer, although it is debatable as to whether such impairment is an etiological factor or a result of the malignant disease. However, it is certain that the immuno-status is further impaired by surgery, radiotherapy or chemotherapy.

PSP has been shown to have immuno-potentiating properties. A preliminary investigation of immunological status in 10 of our patients treated by radiotherapy showed that the 5 patients receiving PSP had marked improvement in the post-radiation period as compared to the 5 controls.

In conclusion, in the pilot studies for PSP done on the clinical level, results have been very encouraging from all the various aspects including clinical effects against tumors, potentiation of effects in radiotherapy, chemotherapy and immunotherapy, as well as adjuvant symptomatic treatment. It is suggested that further Phase III trials be carried out under strict protocol, so that recognition and establishment of PSP as a new anti-cancer weapon will be achieved among oncologists all over the world.

Table 2 Immuno-regulatory action of PSP

	Per cent lymphocyte mitosis		
Treament	Before RT	At end of RT	1 month after RT
Radiation alone	19	12	11.9
Radiation + PSP	18	16	20.0