

IMMUNOTHERAPY OF METASTATIC LUNG AND MALIGNANT BLADDER TUMOR WITH SSM-VACCINE

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INTRODUCTION

Non-specific immunotherapy is currently being used in the treatment of carcinoma. Since BCG-therapy by Mathe et al (1969)¹⁾ and Morton et al (1974)²⁾ was introduced, several immunopotentiators such as Krestin (PSK), Picibanil (OK-432) and BCG-CWS have been developed and clinically tested.

This paper reports excellent results obtained from the use of SSM-Vaccine (Special Substance of Maruyama) in the treatment of a patient with malignant testicular tumor showing pulmonary metastasis. Concurrently reported are favorable responses observed in patients with malignant carcinoma of the bladder and prostate treated with SSM-Vaccine alone.

This paper will also attempt to discuss our view on immunotherapy with SSM-Vaccine.

MATERIAL AND METHOD

Subjects studied: There were a total of 11 case studies consisting of 1 patient with malignant testicular tumor showing lung metastasis and 10 patients with Grade III, Stage D₁-D₂(T₄) malignant tumors of the bladder and prostate.

Immunopotentiator: Special Substance of Maruyama Vaccine was used in the treatment as a single agent. This SSM-Vaccine was first reported in 1966. At the 11th Congress of International Cancer Society held in Florence, Italy in 1973,

clinical results of 2,474 patients treated with this vaccine were presented creating a sensation. SSM-Vaccine is an extract from tubercle bacilli and mostly composed of poly-saccharides such as arabinomannan and 6-0-methylglucose and certain nucleic acids. It is soluble in water and insoluble in ether.

Dosage and Administration: SSM-Vaccine was administered by the subcutaneous injection every other day at a dose of 1.0 ml (1.0 µg) Type A and 1.0 ml (0.1 µg) Type B alternatively. One course of treatment consisted of 10 subcutaneous injections of each type.

RESULTS

1. Malignant Testicular Tumor with Pulmonary Metastasis:

A 34-year old man was admitted with a complaint of painless swelling of the left scrotal content.

He was diagnosed as a left-sided testicular tumor with pulmonary metastasis (Photo. 2). Left orchiectomy was initially performed.

Histological examination of the primary testicular tumor revealed that it was a mixed type of embryonal carcinoma and seminoma (Photo. 1).

After removal of the testicular tumor, he was treated with Liniac (total 3,000 rds) covering inguinal and renal hilus combined with 5-Fluorouracil (total about 1,000 mg).

Then, a treatment with SSM-Vaccine was initiated 6 weeks after operation. During the first 3 months, the metastatic focus in the left lung showed a

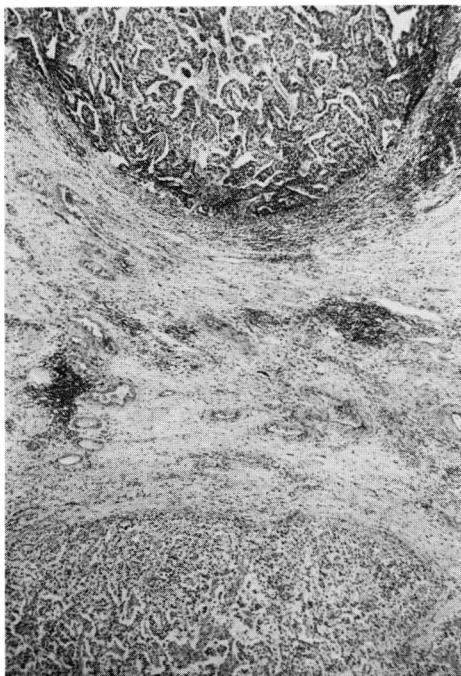


Photo. 1

decrease. Although a part of it revealed a decrease, another part of it an increase or a new metastatic lesion occurred in the right lung (Photo. 3).

At the end of 4 months, however, the metastatic lesion started to disappear and his chest film at 5 months became completely normal (Photo 4). The patient has been doing well thereafter.

It is noted that clinical response and remission correspond well to laboratory findings (Figs 1 and 2).

Table 1 shows the parameters which may reflect the immunoactivity of the patient after the treatment. Unfortunately, pre-treatment data are not available.

Table 1. Peripheral lymphocytes

1. MIGRATION INHIBITION FACTOR (MIF)	94%
2. PHYTOHAEMAGGLUTININ (PHA S.I.)	38.4%
3. T CELL FUNCTION	106%
4. T CELL, HELPER T	58%
SUPPRESSOR T	19%
B CELL	10%
NULL CELL	17%

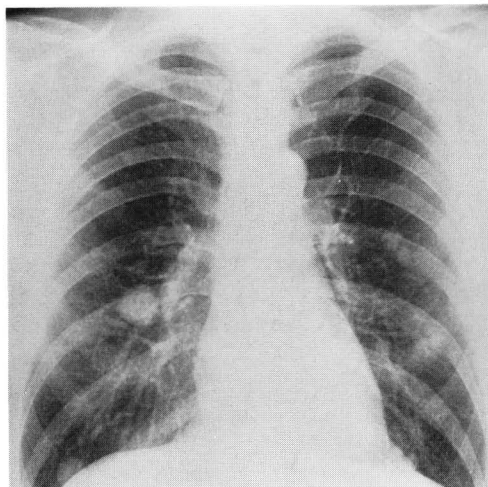


Photo. 2

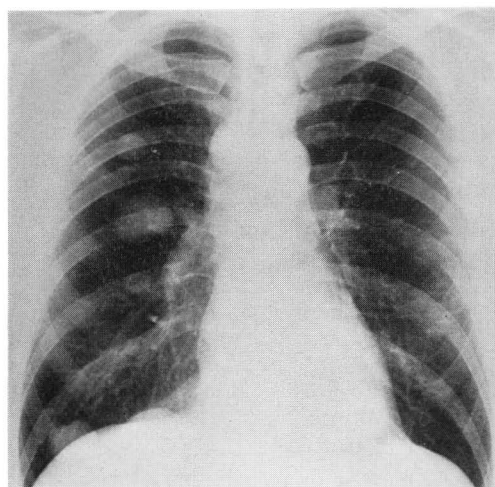


Photo. 3

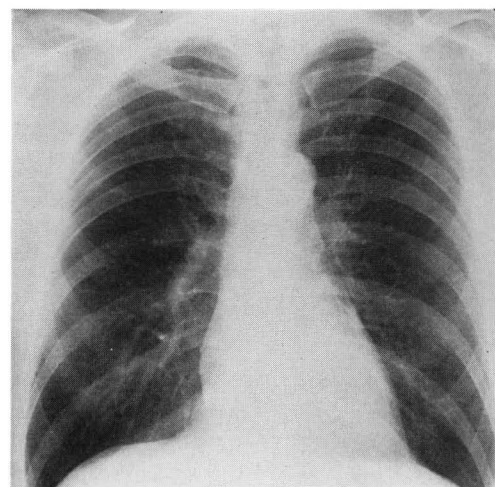


Photo. 4

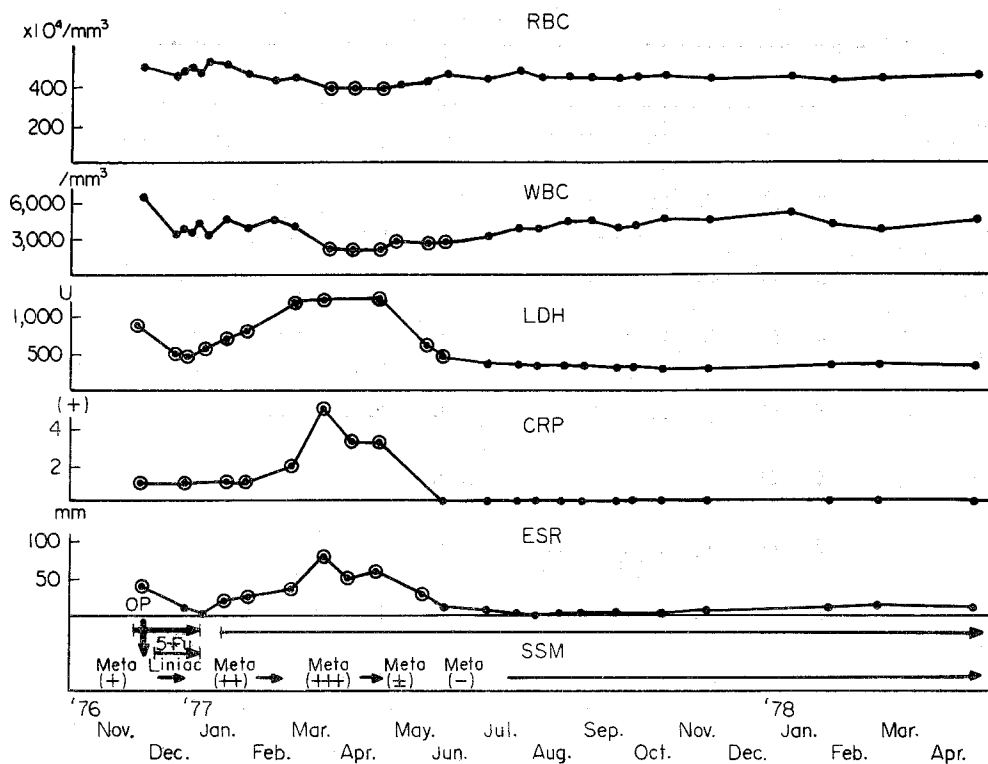


Fig. 1. Some of laboratory findings and their variations

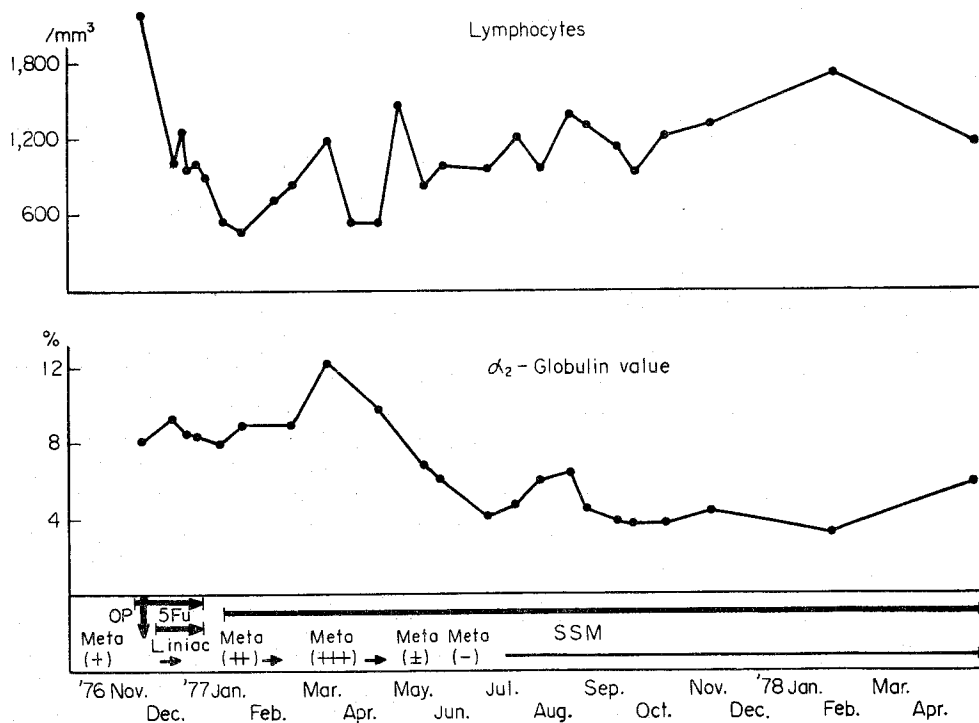
Fig. 2. Lymphocytes and α_2 globulin variations

Table 2. Bladder and prostatic tumor treated by SSM

CASE NO.	AGE	SEX	DIAGNOSIS	PERIODS OF TREATMENT (MONTHS)	RESULTS
1	72	F.	BLADDER TUMOR T ₄ N ₃ M ₀	42 M.	TUMOR GROWING LARGER, STILL ALIVE WITHOUT COMPLAINT
2	77	M.	BLADDER TUMOR T ₄ N ₃ M _{1b}	27 M.	PARTIAL DISTRACTION OF TUMOR, STILL ALIVE WITHOUT ANY COMPLAINT
3	46	M.	BLADDER TUMOR T ₄ N ₃ M ₀	25 M.	COMPLETE DISTRACTION OF TUMOR, STILL ALIVE
4	52	M.	BLADDER TUMOR T ₄ N ₃ M _{1b}	20 M.	SLIGHT DISTRACTION OF TUMOR, STILL ALIVE WITHOUT ANY COMPLAINT
5	62	M.	BLADDER TUMOR T ₄ N ₃ M _{1c}	6 M.	NO EFFECT, DIED
6	62	M.	BLADDER TUMOR T ₄ N ₃ M ₀	20 M.	NO EFFECT, DIED
7	48	F.	BLADDER TUMOR T ₄ N ₄ M _{1d}	13 M.	NO EFFECT, DIED
8	57	M.	BLADDER TUMOR T ₄ N ₂ M ₀	8 M.	NO EFFECT, DIED
9	59	M.	PROSTATIC TUMOR T ₄ N ₃ M _{1d}	5 M.	SIGNIFICANT EFFECT FOR LUMBAR PAIN, DIED WITH BRAIN METASTASIS
10	68	M.	PROSTATIC TUMOR T ₄ N ₄ M _{1d}	3 M.	DISAPPEARANCE IN SEVERE LUMBAR AND BACK PAIN AFTER ONE MONTH THERAPY, DIED AFTER 3 MONTHS

NO SIDE EFFECTS WERE OBSERVED.

2. Malignant Tumors of the Bladder and Prostate:

Table 2 summarizes the results of the treatment of 10 patients with tumors in the bladder and prostate.

CURRENT LITERATURE REVIEW

Recent research studies done in Japan on SSM-Vaccine will be cited before making final remarks on our clinical experience.

H. Kawamura (1977)³⁹ studied effects of Prednisolone, OK-432 and SSM, by using the microplate method, on the PHA reaction of peripheral lymphocytes obtained from 8 healthy volunteers, 3 patients with terminal cancer of the stomach, 3 patients with malignant lymphoma and 1 patient with dermatomyositis. Prednisolone in the concentrations of 0.01~0.05 ug/ml and SSM in 250 ug/ml enhanced the PHA reaction.

In all cases, an enhancement was seen in the decreasing order of SSM>OK-432>Prednisolone.

N. Ishida (1978)⁴⁰ made an experiment in which 0.005~50 mg/kg SSM or PPD was given to BCG sensitized mice (6~8 weeks old DDI mice sensitized with 1 mg BCG by IV injection) and found that a peak 1F production with SSM was at 5 hrs -5 mg/kg while that with PPD was at 3 hrs -0.5 mg/kg (Fig. 3). He postulated that the antitumor activity of SSM would be a host-mediated since R.M. Schults(1977)⁵⁰ also reported that 1F would act on macrophages and activate them to increase their killing activities against tumor cells.

Ishida further studied a relationship between SSM administration, macrophage activation and antitumor activity. He administered to normal mice IP 0.05~50 mg/kg of SSM and extracted macrophages.

He then added FM-3A and L-1D cells, cultured and made time course determination for tagged cells. The results indicated that SSM administered macrophages gave 78.9% phagocytosis while non-administered macrophages gave only 39.4% (Fig. 4).

H. Sato (1979)⁶⁰ postulated that although neoplastic cells generally gave a weak antigenicity and patients with neoplastic disease usually had a low ability to gain immunity to the disease, certain compounds might nevertheless give a necrobiotic condition where increased antigenicity could make immunotherapy possible. He therefore implanted rats with an intravenous dose of 10^7 AH41C, AH66 and AH44 and 3 days after implantation followed by 1.0ml SSM-A once a day subcutaneously or intramuscularly. In each test group, at least 3 rats survived over 60 days. Each test group initially had 6 rats.

On the other hand, test group receiving no SSM-A all died in 20 days. Tumor was completely destructed and its part with capsule in some cases administered subcutaneously. On the other hand, tumor completely disappeared in one case administered intramuscularly. SSM was therefore considered to increase a survival rate.

D. Mizuno⁷² initiated experiments in which he injected 0.04 ml complete Freund's adjuvant containing 350 μ g heat killed BCG to the right hind, amputated the hind 10 days after injection, and implanted subcutaneously 3.0×10^6 Ehrlich 7 days after amputation.

The tumor grew for 31 days in control groups while it grew to a maximum size at the 17th to 21th day in groups receiving SSM-A 1/40 and 1/400 dilutions. It should be noted that SSM-A or saline was administered at 1, 4, 7 and 10th days after implantation and that growth suppression became apparent after the last dose of the drug (Fig. 5).

CONCLUSION

In this paper, we presented a case of testicular tumor with pulmonary metastasis that had remarkable remission with the use

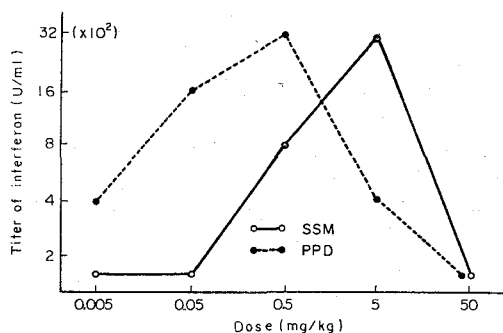


Fig. 3. Dose response of interferon induction with SSM in BCG-sensitized mice

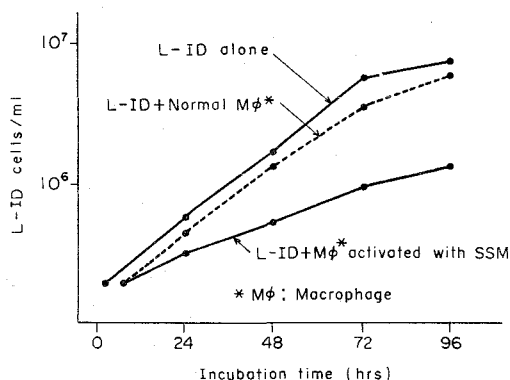


Fig. 4. Effects on growth suppression of tumor cells (L-ID) by macrophages activated with SSM-vaccine

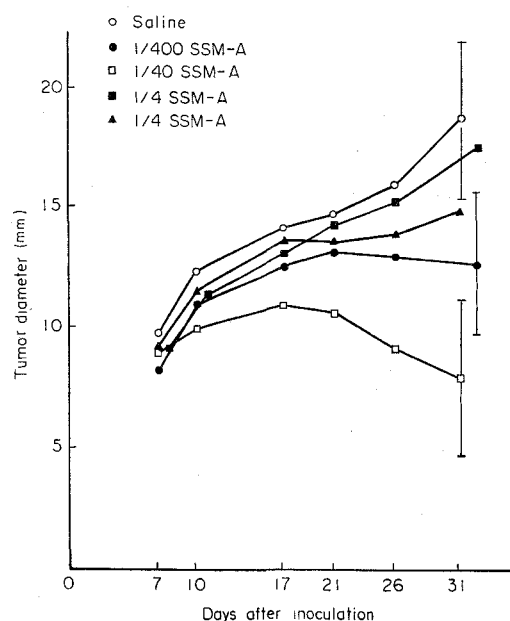


Fig. 5. Growth suppression over Ehrlich by SSM-A in CFA immunized mice

of SSM-Vaccine. We also presented 10 cases with carcinoma in the bladder and prostate treated with SSM-Vaccine.

Chemistry and mechanism of action of SSM-Vaccine will require further investigations. Therefore, we will only attempt to comment from clinical points of view on the value of immunotherapy including SSM-Vaccine.

1. As shown in this paper, excellent clinical results were obtained with immunotherapy.

2. It should be kept in mind that there will no doubt be clinical failures with immunotherapy because both tumor cells and host have their own individual characteristics.

3. Survival period may be expected to be prolonged even if tumor cells and host coexist without complete remission. Y. Yano⁸⁾ reports that a 55-year-old patient with malignant tumor of the common bile duct survives 6 years 3 months with the treatment of the vaccine alone.

4. The use of immunopotentiator increases the host immunity not only to the tumor cells but also to virus, bacteria, fungi, etc. resulting in an increase in survival rate.

5. Immunotherapy requires a continued use of immunopotentiator for certain period of time if a good result is expected to be achieved.

6. SSM-Vaccine alleviates a pain, extends a survival period and gives no side effects. Therefore, it can be administered to patients who are unable to take drugs

because of side effects.

7. Future studies on immunopotentiators should be focused to determine a schedule for combination with other cancer therapies.

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和 文 抄 録

悪性睾丸腫瘍の肺転移ならびに悪性膀胱腫瘍に対する
SSM-vaccine による免疫療法

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われわれは SSM-Vaccine を尿路・性器腫瘍に対し試験的に使用してきたが、最近、悪性の睾丸腫瘍による肺転移に著効がみられた症例を経験したのでその症例を報告する。なお若干の悪性膀胱腫瘍、前立腺腫瘍に対する効果についてもものべる。

さらに本邦における最近の SSM-Vaccine に関する基礎的研究を報告し、SSM 免疫療法についての私見をのべる。

1 ここにしめしたように免疫療法によって著効例がみられた。

2 免疫機構からみて腫瘍細胞あるいは宿主の個性的な相互関係から無効例も当然あると思われる。

3 完全に治癒しなくても腫瘍と宿主との共存による延命効果が期待できる。

4 ウイルス、細菌、真菌などの感染に対する抵抗力の増強も延命効果に関係する。

5 われわれの経験からも言えることであるが、免疫剤の効果を期待するためには一定期間の使用が必要である。

6 SSM-Vaccine の特徴として疼痛の軽減、消失、延命効果さらに副作用のみられないことなどがあげられている。

7 従来の癌治療法と免疫剤の併用に関する基本的なスケジュールが今後、検討されるべきである。

稿を終るにあたり日本医科大学ワクチン療法研究施設の丸山千里名誉教授、藤田敬四郎講師に深謝致します。

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