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

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(Director: Yoshio Iki, M.D.)

INTRODUCTION

Non-specific immunotherapy is currently being used in the treatment of carcinoma. Since BCG-therapy by Mathe et al (1969) and Morton et al (1974) 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 orchectomy 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
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

<p>| | |</p>
<table>
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<tbody>
<tr>
<td>1. Migration Inhibition Factor (MIF)</td>
<td>94%</td>
</tr>
<tr>
<td>2. Phytohaemagglutinin (PHA 5.1.)</td>
<td>38.4%</td>
</tr>
<tr>
<td>3. T cell function</td>
<td>106%</td>
</tr>
<tr>
<td>4. T cell, Helper T</td>
<td>58%</td>
</tr>
<tr>
<td></td>
<td>Suppressor T</td>
</tr>
<tr>
<td>B cell</td>
<td>10%</td>
</tr>
<tr>
<td>NULL cell</td>
<td>17%</td>
</tr>
</tbody>
</table>
Fig. 1. Some of laboratory findings and their variations

Fig. 2. Lymphocytes and α₂ globulin variations
Table 2. Bladder and prostatic tumor treated by SSM

<table>
<thead>
<tr>
<th>CASE NO.</th>
<th>AGE (Y)</th>
<th>SEX</th>
<th>DIAGNOSIS</th>
<th>PERIODS OF TREATMENT (MONTHS)</th>
<th>RESULTS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>72</td>
<td>F</td>
<td>BLADDER TUMOR T_4N_3M_0</td>
<td>42 M.</td>
<td>TUMOR GROWING LARGER, STILL ALIVE WITHOUT COMPLAINT</td>
</tr>
<tr>
<td>2</td>
<td>77</td>
<td>M</td>
<td>BLADDER TUMOR T_4N_3M_1b</td>
<td>27 M.</td>
<td>PARTIAL DISTRACTION OF TUMOR, STILL ALIVE WITHOUT ANY COMPLAINT</td>
</tr>
<tr>
<td>3</td>
<td>46</td>
<td>M</td>
<td>BLADDER TUMOR T_4N_3M_0</td>
<td>25 M.</td>
<td>COMPLETE DISTRACTION OF TUMOR, STILL ALIVE</td>
</tr>
<tr>
<td>4</td>
<td>52</td>
<td>M</td>
<td>BLADDER TUMOR T_4N_3M_1b</td>
<td>20 M.</td>
<td>SLIGHT DISTRACTION OF TUMOR, STILL ALIVE WITHOUT ANY COMPLAINT</td>
</tr>
<tr>
<td>5</td>
<td>62</td>
<td>M</td>
<td>BLADDER TUMOR T_4N_3M_1c</td>
<td>6 M.</td>
<td>No effect, Died</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>M</td>
<td>BLADDER TUMOR T_4N_3M_1b</td>
<td>20 M.</td>
<td>No effect, Died</td>
</tr>
<tr>
<td>7</td>
<td>48</td>
<td>F</td>
<td>BLADDER TUMOR T_4N_3M_2a</td>
<td>13 M.</td>
<td>No effect, Died</td>
</tr>
<tr>
<td>8</td>
<td>57</td>
<td>M</td>
<td>BLADDER TUMOR T_4N_3M_2a</td>
<td>8 M.</td>
<td>No effect, Died</td>
</tr>
<tr>
<td>9</td>
<td>59</td>
<td>M</td>
<td>PROSTATIC TUMOR T_4N_3M_2d</td>
<td>5 M.</td>
<td>SIGNIFICANT EFFECT FOR LUMBAR PAIN, DIED WITH BRAIN METASTASIS</td>
</tr>
<tr>
<td>10</td>
<td>68</td>
<td>M</td>
<td>PROSTATIC TUMOR T_4N_3M_1a</td>
<td>3 M.</td>
<td>DISAPPEARANCE IN SEVERE LUMBAR AND BACK PAIN AFTER ONE MONTH THERAPY, DIED AFTER 3 MONTHS</td>
</tr>
</tbody>
</table>

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) 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 μg/ml and SSM in 250 μg/ml enhanced the PHA reaction.

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

N. Ishida (1978) 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) 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) 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. Mizuno initiated experiments in which he injected 0.04 ml complete Freund's adjuvant containing 350 μg heat killed BCG to the right hind, amputated the hind 10 days after injection, and implanted subcutaneously $3.0 \times 10^6$ 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
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. Yano 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.

REFERENCE


(1980年8月5日受付)
和文抄録

悪性星状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

関東通信病院泌尿器科（部長：生亀芳雄）
生亀 芳雄・小川 秀弥

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だが、最近、悪性の星状腫瘍によ
る肺転移に効果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述べる。

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
を述べる。

1 こことしめたように免疫療法によって著効例
がみられた。

2 免疫機構かえ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の特徴として腫瘍の軽減、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 従来の癌治癒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。

著を執るにあたり日本医科大学ウクレネ研究実施の丸
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