Successful Treatment with a Long-acting Somatostatin Analogue (SMS201-995) in a Patient with Malignant Carcinoid Syndrome

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A case of carcinoid syndrome is presented. Pulmonary adenocarcinoma with hepatic metastasis was found in a 60-year-old Japanese male who was complaining of fever, cough and haemoptysis. After the treatment with 5-fluorouracil (5-FU) over 2 years, he was diagnosed as carcinoid syndrome on the appearance of facial flushing, face edema and watery diarrhea accompanied by high levels of 5-hydroxyindole acetic acid (5-HIAA) in blood and urine. Prednisolone, which was initially effective, was replaced by SMS201-995 due to the considerable dose increase of the former because its effect became insufficient during the course of the treatment. Clinical symptoms were improved by SMS201-995 and blood 5-HIAA level decreased gradually but markedly. Thus better results were obtained by SMS201-995 compared with prednisolone. These results imply that SMS201-995 is appreciated as an effective drug for treatment of carcinoid syndrome.

Key Words: Malignant carcinoid syndrome, Long-acting somatostatin analogue (SMS201-995), 5-hydroxyindole acetic acid (5-HIAA)

The malignant carcinoid syndrome has excited clinical interests and stimulated a therapeutic challenges since it was first described more than 30 years ago. The syndrome is very rare disease, and clinically, it usually presents typical symptoms such as episodic facial flushing and watery diarrhea^{1,2,4)}.

Somatostatin, a tetradecapeptide, a potent growth hormone (GH) inhibitory factor that was discovered in the posterior lobe of the hypothalamic tissue 13 years ago³⁾, is a pharmacological inhibitor of the release of various endogenous peptides such as insulin, glucagon and gastrointestinal peptides⁴⁾. Many investigators have reported the efficacy of somatostatin in carcinoid syndrome, e.g. Dharmasathaphorn et al.⁵⁾ in 1978 on its effectiveness to diarrhea and Frolich et al.⁶⁾ in 1978 on that to facial flushing. Although its clinical use was limited for its quite short half-life

of 3 minutes^{11,12)}, the development of a long-acting somatostatin analogue (SMS201-995, Sandoz, Table 1)¹³⁾ settled this problem. Clinical trials of SMS201-995 in carcinoid syndrome are currently in progress in Japan.

The authors gave SMS201-995 to a patient with malignant carcinoid syndrome of pulmonary origin which had developed 6 years ago and metastasized to liver, and observed marked improvement of clinical symptoms. We will report here the details of this case with some discussion.

CASE REPORT

A 60-year-old Japanese man complained of fever, cough and bloody sputum on February 1981. He was diagnosed as pulmonary adenocarcinoma with hepatic metastasis on March 1981, because of abnormal shadow in the

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lower lobe of left lung on chest X-P (Figure 1), hepatomegaly and hepatic tumors on abdominal ultrasonography (Figure 2) and abdominal computerized tomographic scan (Figure 3) and the results of other examinations. In spite of 5-fluorouracil (5-FU) therapy, facial flushing, face edema and watery diarrhea appeared on December 1983. High blood and urinary levels of 5-hydroxyindole acetic acid (5-HIAA) confirmed the diagnosis of carcinoid syndrome. These symptoms were improved on treatment with tegafur uracil (UFT) and cyclophosphamide (CPM). Although aggravation of these symptoms occurred on September 1985, transient relief was obtained by additional treatment with doxorubicin HCl (ADM) and steroid (prednisolone). However, he was readmitted because of exacerbation of the symptoms and tumor on July 1986.

On admission the *patient* was slightly poor nourished and physical examination revealed facial flushing and edema, marked lacrimation and redness of palpebral and bulbar conjunctiva (Figure 4). Slightly hyperactive bowel sounds were auscultated over the abdomen, and liver was palpable 6cm below the right hypochondrium. Laboratory data disclosed decreases in total protein, albumin, *Ch-E* and serum K and increases in GOT, GPT, LDH and ALP. Endocrinological

data showed slightly high blood serotonin level and markedly high blood and urinary 5-HIAA

Fig. 1. Lateral radiography of the chest indicates a tumor (11.5×7.0×5.5cm) at the area of nine segment of the left lung.

Fig. 2. Abdominal ultrasonography shows hyperechoic and hypoechoic tumors of various size in liver (a), and the bigger tumors are suspected to have developed central necrosis (b). Small amount of ascites is found (c).

Fig. 3. Abdominal computerized tomographic scan (CT scan) shows multiple irregular low density areas of various size in liver, which seem as metastatic tumors.

Table 1. Structure of SMS201-995

Table 2. Laboratory findings on admission

Hematological Examination		Biochemical examination (serum)	
RBC	$436 \times 10^6 / \mu\text{l}$	T.P.	5.2 g/dl
Hb	13.3 mg/dl	Alb	2.8 g/dl
Ht	40.8 %	T-Bil	1.0 mg/dl
WBC	$8080 / \mu\text{l}$	GOT	110 U/L
Plt	$25.2 \times 10^4 / \mu\text{l}$	GPT	57 U/L
ESR	18 mm	LDH	395 U/L
		ALP	193 U/L
		Na	142 mEq/L
		K	2.5 mEq/L
		Cl	108 mEq/L
		BUN	14 mg/dl
		CRP	2.0 mm
Urinalysis		Endocrinological examination	
Protein	(+)	S-Serotonin	0.45 $\mu\text{g/ml}$
Sugar	(-)	S-5 HIAA	1710 ng/ml
		U-5 HIAA	272 mg/day
Tumor Marker			
αFP	3 ng/ml		
CEA	1 ng/ml		

levels (Table 2).

Clinical symptoms were transiently relieved on

Fig. 4. Picture of face before treatment with SMS201-995.

Fig. 5. Picture of face after treatment with SMS201-995.

treatment with prednisolone 60mg/day after admission, but they were aggravated again after dose reduction to 20mg/day. Since prednisolone should be continuously given at rather large dose

for further improvement of the symptoms, SMS201-995 therapy was started on October 14 at the dose of 100 $\mu\text{g/day}$ s.c., in view of side effects. Loose stools, slight facial flushing and face edema were still observed whereas diarrhea stopped on the day after the treatment. Therefore, the dose of SMS201-995 was increased to 200 $\mu\text{g/day}$ on November 8. Thereafter all of these symptoms disappeared and stools were normalized (Figure 5). Circadian changes (Figure 6, 7) in blood GH, insulin and serotonin were hardly affected by SMS201-995 (100 and 200 $\mu\text{g/day}$). Circadian changes in blood 5-HIAA during the

treatment with SMS201-995 (100 $\mu\text{g/day}$) showed a fluctuation pattern similar to the pretreatment one, while it markedly decreased to low level after treatment with SMS201-995 (200 $\mu\text{g/day}$). Since there were many reports^{2,11)} that SMS201-995 alone might not shrink tumors although it could improve clinical symptoms, UFT, CPM and prednisolone were concomitantly used for prevention of abrupt deterioration of symptoms. Since neither subjective nor objective symptoms were observed and general condition was stable after administration of SMS201-995 (200 $\mu\text{g/day}$), prednisolone was discontinued on November 19. After that, aggravation of symptoms or enlargement of tumors did not occurred. Blood serotonin

Fig. 6. Circadian changes in GH and insulin during the treatment with SMS201-995.

Fig. 7. Circadian changes in blood 5-HIAA and serotonin during the treatment with SMS201-995.

Fig. 8. Fluctuations in Serotonin and 5-HIAA after the treatment with SMS201-995.

level which had shown wide variation before the treatment did not show definite tendency after the treatment with SMS201-995 (100 µg/day). High blood and urinary 5-HIAA levels remarkably decreased after the treatment with SMS201-995 (100 µg/day). They reincreased after 1-2 weeks of the treatment with SMS201-995, which decreased again on 200 µg/day. Thereafter, in long-term observation period, blood serotonin has shown a tendency to decrease from the upper limit of normal range while blood 5-HIAA has reduced and kept 1/3 of the pretreatment level (Figure 8). At the present time, 11 months after the SMS201-995 treatment, there is no change in tumor size, and the patient is treated on an outpatient basis.

DISCUSSION

The efficacy of SMS201-995 in the patient with malignant carcinoid syndrome with metastasis to liver was presented. Several isolated reports show that somatostatin or its long-acting analogue (SMS201-995) may improve these symptoms and decrease serotonin and 5-HIAA⁶⁻⁹).

Our patient suffered from facial flushing and watery diarrhea, followed by marked weight loss, ascites and peripheral edema. Prednisolone was effective to those symptoms, but larger dose was required later. The effect gradually became insufficient as a result of frequent dose increase or

decrease, and the risk of side effects increased. All of these problems could be settled by SMS201-995, and better results were obtained than on prednisolone. These results imply that SMS201-995 is a valuable drug for the treatment of carcinoid syndrome.

The pharmacological mechanism of SMS201-995 in carcinoid syndrome has not been clarified, although there has been much discussion concerning the variability of serotonin and 5-HIAA in carcinoid syndrome^{10,11,15}). In the present case, blood 5-HIAA level decreased gradually but markedly after the treatment, which was accompanied by the improvement of clinical symptoms. From these findings, the onset of the clinical symptoms seemed to be closely associated with the secreted 5-HIAA and the severity might be correlated with 5-HIAA level. It was estimated that SMS201-995 might exert inhibitory action on the synthesis or release of serotonin as a mediator of monoamine oxidase activity in the metabolic pathway of tryptophan, and as a result of the inhibition of 5-HIAA secretion, these symptoms might disappear. As above-mentioned, SMS201-995 was quite useful for improvement of clinical symptoms.

The efficacy of SMS201-995 in reduction of the size of the primary or the metastatic tumor has not been established. In this patient, the tumor

size showing an increasing tendency before the treatment with SMS201-995 remained same after the treatment, though the dosages of other antineoplastics were not changed throughout the treatment with SMS201-995. Considering this fact, it seemed that SMS201-995 alone or with some cooperative effect with other antineoplastics might be effective in inhibiting tumor growth and enlargement. Quite few reports show that SMS201-995 is effective for tumor shrinkage^{2, 11)}, so further follow-up of the tumors in this case attracts considerable interest.

CONCLUSION

SMS201-995 was given to a patient of carcinoid syndrome of pulmonary origin which had developed 6 years ago and metastasized to liver. Significant improvement was obtained in clinical symptoms and in laboratory data. In this report, the efficacy of SMS201-995 in carcinoid syndrome was discussed with the review of several references.

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