Case Report

Long-Term Survival in a Patient with Malignant Carcinoid Treated with High-Dose Octreotide

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Octreotide acetate, a long-acting somatostatin analogue, is effective in controlling and markedly reducing the symptoms of carcinoid crisis. We report a patient with carcinoid syndrome with prolonged survival for 4.5 years with high dose octreotide therapy and survived for 7.5 years after the first flushing, in spite of episodes of severe carcinoid crisis. Dose escalation was required in order to control carcinoid symptoms, and the final dosage was 5,950 μg/day. Although administration of such a high dosage of octreotide has never been reported before, we found that octreotide could be used at this dosage safely without inducing serious side effects, and probably prolonged the patient’s survival. Our experience with this case indicates that octreotide acetate is an effective drug in controlling carcinoid crisis and prolonging survival without serious side effects.

Key words: interferon, carcinoid crisis

Introduction

Although malignant carcinoid syndrome is a rare disease and occurs in less than 10% of patients with carcinoid tumors, its clinical symptoms are serious and occasionally life-threatening complications develop. The five-year survival rate of patients with carcinoid syndrome with distant metastasis is 18–21%. A median survival period after the first episode of flushing is reported to be 38 months (1). The median survival period in patients with inoperable tumors or with urinary 5-hydroxyindole acetic acid (5-HIAA) in excess of 150 mg/24 h is only 11 months (2). Although antineoplastic chemotherapy has been used as a therapy for carcinoid syndrome, its objective response rate is only 20–30% (3). While natural somatostatin is effective in controlling carcinoid crisis, it must be continuously intravenously infused because of its short half-life of less than two minutes. On the other hand, octreotide acetate, a long-acting somatostatin analogue, is a synthetic octapeptide containing two D-amino acids that mimics the active site of somatostatin. The more specific and more prolonged action of this octapeptide in controlling carcinoid crisis is considered to consist of blockade of hormone release and peripheral actions (2). Many cases of successful treatment of carcinoid with octreotide have recently been reported (2–7), although in none of them was the dosage as high as that in the present case.

Case Report

In February 1981, a 56-year-old Japanese man complained of fever and cough with hemoptysis. In March, pulmonary unclassified carcinoma with hepatic metastasis was diagnosed based on computed tomographic scans and histological findings of a hepatic needle biopsy specimen. In December 1983, the patient experienced an episode of cutaneous flushing, facial edema, high fever and watery diarrhea. Bronchial malignant carcinoid with hepatic metastasis was rediagnosed based on the findings of an elevated plasma level of 5-HIAA (400 ng/ml, normal range: 3.6–21.5 ng/ml) and clinical symptoms. Tegafur uracil (UFT), cyclophosphamide (CPA), doxorubicin HCl (ADM), and prednisolone (PSL) were given, and the patient’s clinical symptoms improved. However, he was readmitted because of increase in the severity of these symptoms and progression of the liver metastasis in July 1986. Subcutaneous administration of octreotide at 100 μg/day along with UFT, CPA and PSL was begun in October. The episodes of flushing and watery diarrhea disappeared, and the serum level of 5-HIAA (1,685 μg/ml) also decreased to 437 μg/ml. After this carcinoid crisis, seven episodes of severe crisis occurred. Those
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during the last four years of the patient’s life were particularly severe, with high 5-HIAA level in serum (maximum, 7,260 ng/ml) and urine (maximum, 740 ng/ml). Upon each recurrence, the dosage of octreotide was increased to control symptoms; the maximum dosage was 5,950 ng/day in 1990 (Fig. 1).

In each crisis, 5-HIAA level in serum (Fig. 1) and urine was decreased by increasing the dosage of octreotide from 7,095 ng/ml to 318 ng/ml in the serum in the crisis of 1989, from 7,260 ng/ml to 383 ng/ml in serum in the crisis of 1990 and from 404 to 131 ng/ml and from 740 ng/ml to 218 ng/ml in urine in 1990. Each time an increase in the octreotide dosage of 300–1,500 µg/day was necessary. After the dosage was increased and the crisis controlled, a decrease in the dosage was attempted. But this was not successful, because the decrease of octreotide of 100–200 µg/day brought on another crisis.

When the dosage of octreotide reached 2,000 µg/day, the serum level of TSH, T3 and T4 was decreased (TSH: less than 0.2 µU/ml, T3: 58 ng/dl, T4: 4.8 µg/dl). The secondary hypothyroidism could be controlled with levothyroxine sodium (max 0.1 mg). As the plasma level of TSH sometimes recovered to a normal level after the first episode of hypothyroidism, his hypothyroidism was considered to be reversible. A decrease in the plasma level of ACTH was also observed, and the plasma level recovered to normal with TSH. With the escalation of the dosage of octreotide, fat malabsorption developed and the patient complained of abdominal discomfort and pain at the injection site.

Although the patient began treatment with recombinant alpha interferon at 6 million units daily in November 1990, the tumor size did not decrease nor were the symptoms of carcinoid syndrome improved. In 1991, his general condition gradually deteriorated and liver failure developed due to extended liver metastasis. Despite treatment for liver failure, he went into hepatic coma and died on March 18, 1991, 10 years after his first admission.

Autopsy was performed two hours after death. The liver was markedly enlarged and weighed 4,190 g. Most of the tissue was replaced by metastatic nodules. A number of metastatic foci were also noted in lung, omentum and lumbar vertebrae. The histological findings were the same as the findings of biopsy, showing a trabecular, ribbon-like growth pattern, and the tumor cells had uniformly round nuclei with thin cytoplasm including argyrophilic granules. The thyroid and adrenal gland was of average size. Many small bilirubin stones were in the gallbladder.

Discussion

This patient survived for 7.5 years after the first flushing, 4.5 years of which time he was treated with the long-acting somatostatin analogue, octreotide acetate, in spite of several life-threatening carcinoid crises. Recently, octreotide has come to be commonly used in patients with carcinoid syndrome. It is considered that the octreotide acetate inhibits the release of serotonin and other neurohormones from carcinoid tumor (8, 10).

Most treatment is successful and prevents life-threatening carcinoid crises at the daily subcutaneous dosage of 150–500 µg (in some cases dosage is as high as 1,500 µg/day) (2–4, 6–9). In the present case, octreotide also markedly reduced the severity of carcinoid crisis, decreased 5-HIAA secretion, improved clinical symptoms, and prolonged survival, while maintaining good quality of life.

The dose required to control the carcinoid crises increased progressively. A decrease in the dosage of octreotide was attempted after each crisis was finished. But whenever the dosage of 100 or 200 µg/day was decreased, another crisis...
occurred. Thus it was impossible to decrease the dosage of octreotide. The final maximum dose reached 5,950 μg/day; use of such a high dosage of octreotide for carcinoid syndrome has never been reported. Reported side effects of octreotide include fat malabsorption, pain at the injection site, rash, nausea, vomiting, abdominal discomfort, dizziness and headache (4, 5, 8). In the present patient, fat malabsorption was observed, and the patient complained of pain at the injection site and abdominal discomfort. He also had cholelithiasis (asymptomatic). Octreotide has been reported to inhibit the release of various hormones such as growth hormone (GH), thyrotropin (TSH), ACTH, insulin and others (7, 8, 10). In the present case, inhibition of the release of TSH (secondary hypothyroidism) and ACTH was observed at the dosage of 2,000 μg/day of octreotide. Though the dosage of octreotide was increased, the serum level of TSH and ACTH sometimes recovered to a normal level together. This might depend on the tolerance of the patient to octreotide and the inhibition of the release of these hormones was not irreversible.

None of these side effects are life threatening and can be managed with dose adjustments. No evidence of serious hematological, neurological, or renal toxicity was observed, autopsy revealed no evidence of severe side effects, and the high dosage was not associated with any serious side effects. Our experience indicates that octreotide is very useful and safe in controlling and reducing the severity of carcinoid crisis, and can prolong the survival of a patient with carcinoid syndrome. It can be used to decrease the symptoms in patients with carcinoid crisis and a poor clinical condition such as severe dehydration, acidosis or hypokalemia, without the induction of any life-threatening side effect. The only major drawback was that dosage escalation was required to control carcinoid crisis as the tumor size increased (9). The escalation might in part depend upon the tolerance to octreotide which has been previously reported (3). Even though an antineoplastic activity of octreotide has been proposed (5), in the present patient, it neither reduced the tumor size nor did it have an influence on the histological form. This suggests that its antineoplastic activity is limited.

In conclusion, the somatostatin analog, octreotide, is very efficient in reducing and controlling the symptoms of carcinoid crisis, and probably prolonged the survival in the present case. We observed no significant side effects even at a very high dose and after long-term usage. High-dose octreotide therapy may be necessary for controlling carcinoid symptoms and for survival prolongation in the advanced stage.

References