Clinical Efficacy and Safety of Octreotide (SMS201-995) in Terminally Ill Japanese Cancer Patients with Malignant Bowel Obstruction

Yasuo Shima1,5, Atshushi Ohtsu2, Kuniaki Shirao3,6 and Yasutsuna Sasaki4,7

1Palliative Care Unit, National Cancer Center Hospital East, Chiba, 2Division of Gastrointestinal Oncology, National Cancer Center Hospital East, Chiba, 3Division of Gastrointestinal Oncology, National Cancer Center Hospital, Tokyo and 4Division of Oncology/Hematology, National Cancer Center Hospital East, Chiba, Japan

Received February 28, 2008; accepted April 10, 2008

Objective: In patients with advanced cancer, malignant bowel obstruction (MBO) causes gastrointestinal symptoms such as nausea and vomiting leading to severely impaired oral food intake. Thus, MBO markedly diminishes the quality of life (QOL) of these patients because placement of a nasogastric tube becomes necessary. Many studies have shown that octreotide (SMS201–995; SMS), a synthetic analog of somatostatin, is effective for controlling the symptoms of MBO. This study was conducted to assess the efficacy and safety of 300-μg/day initial dose of SMS in Japanese patients with MBO and to investigate the clinical benefit of patients achieved by the improvement of nausea/vomiting based on subjective assessment.

Methods: The subjects were patients with MBO that was refractory to other medical treatment and who had suffered at least two vomiting episodes per day for two consecutive days or had required a nasogastric tube. After enrollment, patients received SMS (300 μg/day) subcutaneously as a continuous injection for 6 days. Patients who responded to this 6-day course of treatment continued to receive the drug.

Results: Among 25 patients who were enrolled, 11 (44.0%) responded to treatment with resolution or improvement of nausea/vomiting. Their symptomatic improvement was assessed by quantitatively measuring the level of control of nausea/vomiting and by using a self-administered QOL questionnaire that evaluated the frequency and severity of nausea/vomiting, the proportion of patients enjoying recreational activities and the overall patient satisfaction with the therapy. SMS was well tolerated, and nausea and agitation were the only adverse events potentially related to this drug.

Conclusion: The results of the study confirmed that the 300-μg/day dose of SMS is safe and effective for patients with MBO uncontrolled by other therapies and suggested that the relief of symptoms with nausea/vomiting by SMS could contribute to improvement of the QOL of patients.

Key words: malignant bowel obstruction – octreotide – terminally ill cancer patients

INTRODUCTION

In patients with advanced cancer, malignant bowel obstruction (MBO) occurs primarily due to carcinomatosis because of the recurrence of gastrointestinal or ovarian cancer. Surveys performed at palliative care facilities of Japan have shown that the incidence of MBO is 10–16% (1,2), which is similar to that reported in the USA and Europe (3–5). Current treatments for MBO include (i)
PATIENTS AND METHODS

Patients in this study were required to be hospitalized, to be between 20 and 74 years of age, to suffer from MBO that was refractory to medical treatment and to have a life expectancy of at least 3 weeks. Before being enrolled in this study, the patients also had at least two episodes of vomiting per day on two designated days or had marked drainage of bowel contents (≥500 ml/day) from a nasogastric tube. Patients who retained hepatic function, as indicated by a total bilirubin ≤2.0 mg/dl, were eligible for the study. The study excluded patients with serious complications (e.g., active infection, pleural effusion and gastrointestinal hemorrhage) and those with symptomatic brain metastasis.

After enrollment, patients received SMS (300 µg/day) subcutaneously as a continuous injection for 6 days. Patients who responded to this 6-day course of treatment continued to receive the drug. The dose of SMS was to be decreased to 150 µg/day in the event of Grade 2 or worse adverse events or if there was marked aggravation of nausea/vomiting.

Patients were assessed daily to determine the number of vomiting episodes, the severity of their nausea and (if relevant) the volume of fluid draining from the nasogastric tube. The volume of intravenous and oral fluid was also measured daily because of a probable influence on the volume of vomitus and tube drainage. The clinical benefit of treatment was also assessed daily during the 6-day treatment period using a self-administered QOL questionnaire (see Appendix 1). Patients were asked about the frequency and severity of nausea/vomiting, the intensity of pain, the amount and quality of sleep and the extent of their enjoyment of recreational activities (TV/radio, reading and conversation).

Response criteria were based on the change from baseline (24 h before the start of treatment) to Day 6 in the severity of nausea/vomiting graded using the Toxicity Criteria of the Japan Clinical Oncology Group (JCOG) (11). Grading of vomiting by JCOG Toxicity Criteria is shown in Table 1. As shown in Table 2, the response to treatment was graded using three categories ['complete control' (CC), 'partial control' (PC) and 'no control' (NC)]. Patients with JCOG Grade 0 nausea/vomiting on Day 6 were assigned a rating of CC. The rating was PC if the JCOG grade for nausea/vomiting was decreased by one grade or more from baseline on Day 6. No change or an increase of JCOG grade was regarded as NC.

In patients with a nasogastric tube at baseline, extubation was allowed if drainage was reduced to >500 ml/day. After extubation, the response to the treatment was graded according to the following three categories defined by the JCOG grade of nausea/vomiting on Day 6: CC (JCOG Grade 0), PC (only one episode of vomiting per day or nausea only) and NC (nausea/vomiting ≥JCOG Grade 2).

The occurrence of adverse events and abnormal laboratory findings were considered for the evaluation of safety, and the severity of adverse drug reaction was grades in accordance with JCOG criteria.

With regard to the clinical laboratory testing, hematology, biochemistry and urine tests were performed just before the start of the treatment with study medication and after 7 days of treatment.

This study was approved by the institutional review board of the National Cancer Center and was conducted in compliance with the Japanese Good Clinical Practice Guidelines. In
accordance with the Declaration of Helsinki, written informed consent was obtained from all patients prior to enrollment.

RESULTS

Twenty-five patients were enrolled and treated with SMS. Their demographic and baseline characteristics are summarized in Table 3. There were 11 men and 14 women with ages ranging from 41 to 67 years (median: 53 years). Gastric cancer was the most frequent type of malignancy (n = 14; 56.0%), followed by colon, ovarian and pancreatic cancer. At baseline, a nasogastric tube was already inserted in eight patients (32.0%) but not in 17 patients (68.0%). The baseline performance status (PS) was 3–4 in 21 patients (84.0%). None of the subjects needed dose reduction to 150 μg/day according to the protocol criteria.

RESPONSE

The response to treatment is summarized in Table 4. Among the 25 patients treated, five (20%) had a response of CC and six (24%) had a response of PC with an overall response rate (CC plus PC) of 44% (95% confidence interval: 24.4–65.1%). Among the 17 patients without a nasogastric tube at baseline, three (17.6%) achieved CC and five (29.4%) achieved PC with an overall response rate of 47.1%. Among the eight patients with a nasogastric tube at baseline, two (25%) achieved CC and one (12.5%) achieved PC with an overall response rate of 37.5%.

In the entire study population, the median number of vomiting episodes per day was significantly reduced from 6.0 (range: 2.0–55) at baseline to 2.5 (range: 0–29) on Day 6 (P = 0.0024). Among the eight patients with a nasogastric tube at baseline, four showed a marked decrease in drainage on Day 2 (Fig. 1). All of the three responders (with a rating of CC or PC) in this subgroup showed a reduction in drainage that was sufficient for extubation and achieved symptomatic improvement.

After 6 days (144 h) of continuous therapy, 14 patients were judged to require further treatment with SMS. Treatment was continued for up to 46 days, with the median duration being 8 days.

CLINICAL BENEFIT (SUBJECTIVE ASSESSMENT)

Subjective clinical assessment was done by an investigation of four categories (Appendix 1). Twenty-three of the 25 patients completed the self-administered questionnaire. The other two patients were unable to complete this questionnaire because of their poor general condition. In addition, the number of responders decreased to 16 patients on Day 6 because of disease progression. The efficacy of SMS was reflected by an improvement of QOL in terms of nausea/vomiting and enjoyment in activities.

SEVERITY OF NAUSEA/VOMITING

At baseline, 11 of 23 patients (47.8%) had moderate or severe nausea/vomiting. On Day 6, only six of 16 patients (37.5%) still had moderate nausea/vomiting and no patient

Table 3. Demographic and baseline characteristics of the patients

<table>
<thead>
<tr>
<th>Variable</th>
<th>Patients (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>11 (44.0)</td>
</tr>
<tr>
<td>Female</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Age (years)</td>
<td></td>
</tr>
<tr>
<td>Range</td>
<td>41–67</td>
</tr>
<tr>
<td>Median</td>
<td>53</td>
</tr>
<tr>
<td>Diagnosis of primary tumor</td>
<td></td>
</tr>
<tr>
<td>Gastric cancer</td>
<td>14 (56.0)</td>
</tr>
<tr>
<td>Colon cancer</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Ovarian cancer</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Cervical cancer</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>Complication(s)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>16 (64.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>9 (36.0)</td>
</tr>
<tr>
<td>Nasogastric tube at baseline</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>17 (68.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>8 (32.0)</td>
</tr>
<tr>
<td>Previous gastrectomy</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>18 (72.0)</td>
</tr>
<tr>
<td>Partial</td>
<td>2 (8.0)</td>
</tr>
<tr>
<td>Total</td>
<td>5 (20.0)</td>
</tr>
<tr>
<td>Surgical treatment of bowel obstruction</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>21 (84.0)</td>
</tr>
<tr>
<td>Yes</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>PS at baseline</td>
<td></td>
</tr>
<tr>
<td>PS 1</td>
<td>1 (4.0)</td>
</tr>
<tr>
<td>PS 2</td>
<td>3 (12.0)</td>
</tr>
<tr>
<td>PS 3</td>
<td>17 (68.0)</td>
</tr>
<tr>
<td>PS 4</td>
<td>4 (16.0)</td>
</tr>
<tr>
<td>PS, performance status.</td>
<td></td>
</tr>
</tbody>
</table>

Table 4. Response

<table>
<thead>
<tr>
<th>Rating</th>
<th>CC (%)</th>
<th>PC (%)</th>
<th>NC (%)</th>
<th>Not evaluated (%)</th>
<th>Total (%)</th>
<th>Response rate (CC + PC), % (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nasogastric tube (–)</td>
<td>5 (20.0%)</td>
<td>6 (24.0%)</td>
<td>13 (52.0%)</td>
<td>1 (4.0%)</td>
<td>25</td>
<td>44.0 (24.4–65.1)</td>
</tr>
<tr>
<td>Nasogastric tube (+)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>At baseline</td>
<td>3 (17.6%)</td>
<td>5 (29.4%)</td>
<td>8 (47.1%)</td>
<td>1 (5.9%)</td>
<td>17</td>
<td>47.1 (23.0–72.2)</td>
</tr>
<tr>
<td></td>
<td>2 (25.0%)</td>
<td>1 (12.5%)</td>
<td>5 (62.5%)</td>
<td>0 (0%)</td>
<td>8</td>
<td>37.5 (8.5–75.5)</td>
</tr>
</tbody>
</table>

CI, confidence interval.
rated nausea/vomiting as severe. Nausea/vomiting was absent or slight in nine of 16 patients (56.3%) on Day 6 compared with eight of 23 patients (34.8%) at baseline.

**CHANGE OF NAUSEA/VOMITING RELATIVE TO BASELINE**

Nausea/vomiting was markedly or moderately alleviated in 11 of 23 patients (47.8%) on Day 1 and in 10 of 16 patients (62.5%) on Day 6.

**ENJOYMENT OF RECREATIONAL ACTIVITIES**

Recreational activities were never or hardly ever enjoyed by seven of 16 patients (43.8%) on Day 6 compared with 15 of 23 patients (65.2%) at baseline. The percentage of patients with fair or modest enjoyment of recreational activities increased from 17.4% (four of 23 patients) at baseline to 43.8% (seven of 16 patients) on Day 6. Figure 2 shows the changes in patients in the individual rating categories during SMS treatment (Days 1–6).

**SAFETY**

Adverse events occurred in nine patients. Among these, only two events in two patients (8.0%) (Grade 1 nausea and Grade 2 agitation) were judged to be potentially related to SMS. Potential treatment-related laboratory adverse events occurred in six patients (26.1%), including thrombocytopenia, leukocytosis, increased ALP and increased γ-GTP. Thus, treatment with SMS was well tolerated and did not cause any serious or clinically significant adverse reactions.

**DISCUSSION**

Many recent studies have shown that SMS is useful for controlling gastrointestinal symptoms due to MBO in patients who have advanced cancer. In this study, we evaluated the efficacy and safety of 300-mg/day initial dose of SMS in Japanese patients with MBO. The primary efficacy endpoint was the change in vomiting episodes after treatment. To ensure objectivity of assessment, we used the JCOG Toxicity Criteria to grade the severity of emesis. In contrast, previous clinical studies have often used the World Health Organization (WHO) Toxicity Criteria (7) (Grade 1: nausea; Grade 2: transient vomiting; Grade 3: vomiting requiring therapy and Grade 4: intractable vomiting). Compared with the WHO criteria, the JCOG criteria (Grade 1: only nausea; Grade 2: 1–5 vomiting episodes per 24 h; Grade 3: ≥6 vomiting episodes per 24 h) seem to provide a more quantitative assessment of the severity of emesis. In this study, we also assessed the clinical benefit of treatment by using a self-administered QOL questionnaire. No previous clinical studies of SMS have included subjective assessment of efficacy by the patients. This is probably because of only a few eligible patients (e.g. terminally ill cancer patients) were in a satisfactory condition to answer a self-administered questionnaire. This was emphasized by the smaller number of respondents on Day 6 (n = 16) compared with baseline (n = 23) in our
Clinical efficacy and safety of octreotide

study. As a result of previous findings and in consideration of the target disease (MBO refractory to other medical treatment), SMS was administered at 300 μg/day (the maximum effective dose) as a 24-h continuous subcutaneous injection using a pump. Dose escalation was not planned or performed because previous studies have shown that there is no significant additional benefit of higher doses.

Forty-four percent of the patients in this study responded to the treatment with SMS, and the overall response rate was slightly lower than that reported previously (5–10,12–14). Possible explanations for the less favorable response to SMS in the present study include differences in the general condition (poor PS), the underlying malignancies and the timing for assessment of the response to treatment.

Regarding the type of underlying malignancies, more than half of the patients enrolled in the present study had gastric cancer (n = 14; 56.0%). Analysis of response data obtained in this study revealed that five of the 14 patients with gastric cancer (35.7%) and six of the 11 patients with other cancer (54.5%) had a response of PC or better. Gastric cancer patients tended to have a lower response rate. Gastric cancer is a common malignancy in the Japanese population, but few earlier studies of SMS have involved patients with gastric cancer. Thus, the lower response rate of gastric cancer patients was partly responsible for the lower overall response rate in the present study.

The timing of assessment might also have affected the difference in the response rate. In this study, we assessed an estimate of response to SMS after 6 days of treatment by comparing the severity of nausea/vomiting as graded according to JCOG Toxicity Criteria between Days 0 (24 h before the starting treatment) and 6. The timing of assessment was based on the results of previous studies (6,7), which suggested no significant difference between the response on Day 6 (144 h) and the response observed over a longer treatment period. However, post hoc analysis of our data revealed that the comparison between Days 0 and 6 did not provide an accurate estimate of the response to SMS in some patients. In fact, the benefit of SMS could not be assessed correctly by Day 6 (the study endpoint) in some of the patients because of worsening of their symptoms due to disease progression. In overseas clinical studies (12,13), the response to SMS was assessed after only 3 days of treatment, so the longer treatment period before examination in this study might also have contributed to the lower response rate.

The patients’ assessment of clinical benefit of treatment in terms of relief of gastrointestinal symptoms showed that the nausea/vomiting status tended to improve similarly to the assessments on JCOG Toxicity Scale, and the percentage of patients enjoying TV, radio, reading and conversation with others was particularly increased. The increase became progressively greater on each day of the 6-day treatment period (Fig. 2), suggesting that symptomatic improvement achieved by SMS may be associated with an improvement of QOL.

Initial treatment with 300 μg/day of SMS for 6 days was confirmed to be effective and safe for the controlling nausea/vomiting in Japanese patients with MBO. Further studies will be performed to evaluate the SMS therapy with respect to the duration of treatment, effect of higher doses and the usefulness of SMS treatment in relation to the location of obstruction in the upper or lower gastrointestinal tract, and investigation should be performed in more patients.

Further studies may also include assessment on Day 4 after 3 days of SMS treatment as done by Ripamonti co-workers (12–13) in overseas clinical study of SMS.

Acknowledgements
The authors are grateful to the patients and physicians who participated in this study, and are particularly indebted to Drs. E. Ariga, H. Minami, H. Fujii, Y. Matsumura and K. Muro from the National Cancer Center East/Central Hospital, Japan.

Funding
This study was sponsored by Novartis Pharma, Japan.

Conflict of interest statement
None declared.

References
13. Mercadante S, Ripamonti C, Casuccio A, Zecca E, Groff L. Comparison of octreotide and hyoscine butylbromide in controlling...


**APPENDIX**

QOL QUESTIONNAIRE

Date:

- Question 1: How intense is your pain?
  (1) None
  (2) Slight
  (3) Moderate
  (4) Severe
- Question 2: How many vomiting episodes do you have per day?
- Question 3: How severe is your nausea and vomiting?
  (1) None
  (2) Slight
  (3) Moderate
  (4) Severe
- Question 4: Did the severity of your nausea and vomiting change after the start of the clinical trial?
  (1) Markedly improved
  (2) Moderately improved
  (3) Unchanged
  (4) Worse
- Question 5: How is your sleep quality?
  (1) Good
  (2) Fair
  (3) Poor
  (4) No sleep
- Question 6: Can you enjoy watching TV, listening to the radio, reading a book, or talking with others?
  (1) Fairly often
  (2) Moderately often
  (3) Hardly ever
  (4) Never