VOLUME 22 · NUMBER 2 · JANUARY 15 2004

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

Octreotide Alone or With Prednisone in Patients With Advanced Thymoma and Thymic Carcinoma: An Eastern Cooperative Oncology Group Phase II Trial

Patrick J. Loehrer Sr, Wei Wang, David H. Johnson, and David S. Ettinger

From the Indiana University Medical Center and The Walther Cancer Institute, Indianapolis, IN; Harvard School of Public Health and Dana-Farber Cancer Institute, Boston, MA; Vanderbilt University, Nashville, TN; and The Johns Hopkins University, Baltimore, MD.

Submitted February 10, 2003; accepted October 31, 2003.

Supported in part by the National Cancer Institute grant U 10 CA 21115 (to the Eastern Cooperative Oncology Group), CA 23318 (ECOG Statistical Center), 2 R 35 CA 39844-08, and the Cancer Center Support grant P 30 CA 82709-04 and R 10 CA 28171-04 from the Public Health Service.

Presented in part at the 38th American Society of Clinical Oncology Annual Meeting, Orlando, FL, May 18-21, 2002.

Authors' disclosures of potential conflicts of interest are found at the end of this article.

Address reprint requests to Patrick J. Loehrer Sr, MD, Indiana Cancer Pavilion, 535 Barnhill Dr, Room 473, Indianapolis, IN 46202; e-mail: ploehrer@iupui.edu.

0732-183X/04/2202-293/$20.00

DOI: 10.1200/JCO.2004.02.047

ABSTRACT

Purpose
To determine the objective response rate, duration of remission and toxicity of octreotide alone or with the later addition of prednisone in patients with unresectable, advanced thymic malignancies in whom the pretreatment octreotide scan was positive.

Patients and Methods
Forty-two patients with advanced thymoma or thymic carcinoma were entered onto the trial, of whom 38 were fully assessable (one patient had inconclusive histology; three patients had negative octreotide scan). Patients received octreotide 0.5 mg subcutaneously tid. At 2 months, patients were evaluated. Responding patients continued to receive octreotide alone; patients with progressive disease were removed from the study. All others received prednisone 0.6 mg/kg orally qid for a maximum of 1 year.

Results
Two complete (5.3%) and 10 partial responses (25%) were observed (four partial responses with octreotide alone; the remainder with octreotide plus prednisone). None of the six patients without pure thymoma responded. The 1- and 2-year survival rates were 86.6% and 75.7%, respectively. Patients with an Eastern Cooperative Oncology Group performance status of 0 lived significantly longer than did those with a performance status of 1 ($P = .031$).

Conclusion
Octreotide alone has modest activity in patients with octreotide scan–positive thymoma. Prednisone improves the overall response rate but is associated with increased toxicity. Additional studies with the agent are warranted.

J Clin Oncol 22:293-299. © 2004 by American Society of Clinical Oncology

INTRODUCTION

Thymic malignancies represent the most common tumor of the anterior mediastinum in adults. The primary treatment of thymoma and thymic carcinoma is surgical resection. More than 90% of patients with encapsulated thymoma are cured with complete surgical extirpation of disease. For patients with locally advanced or metastatic disease, systemic chemotherapy such as cisplatin, doxorubicin, and cyclophosphamide (PAC) is associated with a 50% to 90% objective response rate and a 30% to 50% 5-year survival. Despite high response rates, many patients with advanced thymoma relapse are candidates for salvage therapy. Case reports in small series have documented objective response rates with various drugs such as ifosfamide, fluorouracil, and suramin [1,2].

Somatostatin (SST) receptors have been found to be expressed in a variety of normal and malignant tissues including the thymus [3]. SST receptor scintigraphy with radiolabeled octreotide has been used to localize various tumors. Lastoria et al [4] evaluated indium-111–diethylenetriamine pentaacetic acid–D-Phe^1–octreotide scintography in 18 patients with thymic masses. Uptake was increased (variably defined) in thymoma patients compared with those patients with thymic hyperplasia or other benign disorders. Metastases more than 1.5 cm

were detected at 6 hours or during 24 hours, but small metastatic pleural and pericardial metastases were not universally visualized.

Octreotide is an octapeptide SST analog that has a high affinity for a selective SST subtype (SST_2) receptor. In normal human thymus, the thymic epithelial cells seem to be the major site of the SST production. Ferone et al [5] noted an in vitro inhibitory effect of octreotide on thymic epithelial cells perhaps through blockage or inhibition of the insulin-like growth factor 1 (ILGF-1) and epidermal growth factor. Fuller and Veriti [6] also verified the importance of the interaction of the thymus with SST, which they postulated had an impact on the T-lymphocyte development through a paracrine mechanism by SST. Growth hormone and other cytokines may also affect thymic epithelial cell proliferation in vitro [7,8].

In 1998, Palmieri et al [9] reported a complete remission in a patient with thymoma and pure red cell aplasia who was previously treated with octreotide and prednisone. Because prednisone has a lympholytic effect that might diminish the size of a tumor without affecting the malignant epithelial component, the contribution of octreotide was uncertain. To evaluate the duration of the objective response rate of remission and toxicity of octreotide, the Eastern Cooperative Oncology Group (ECOG) initiated a phase II trial. Patients were initially treated with octreotide alone, and if they did not respond, prednisone was added after two cycles of therapy. As such, the subsequent response rate and toxicity to prednisone added to octreotide was also evaluated.

PATIENTS AND METHODS

Patients with histologic or confirmed invasive, recurrent, or metastatic thymoma or thymic carcinoma not amenable to curative therapy were eligible for this trial. Patients must have had extensive disease, defined as disease outside the mediastinum and (in patients with prior radiation therapy) disease that had progressed in sites of prior radiotherapy. Patients with prior chemotherapy were eligible. Patients with prior radiotherapy were eligible if tumor grew in an area of prior radiation or in a metastatic site before study entry. In addition, patients must have had adequate hepatic function (serum bilirubin < 2.0 mg/dL), renal function (serum creatinine ≤ 3.0 mg/dL), and an ECOG performance status of 0 or 1. Patients receiving corticosteroids for myasthenia gravis received the same dosage of corticosteroids and were eligible for this trial. All patients must have had a radionuclide octreotide scan that demonstrated activity in the sites of measurable disease (it was not required that all disease have active update by octreotide scan). Patients with acute intracurrent complications (such as infections, postsurgical complications, or diabetes mellitus) or other contraindications to high-dose corticosteroid therapy were ineligible. Patients had to be older than 18 years of age and sign a written informed consent.

All eligible patients were subsequently treated with octreotide in a dose of 0.5 mg subcutaneously tid for a maximum of 1 year. One month of therapy equaled a treatment cycle. Patients in a complete or partial remission at the end of two treatment cycles of therapy continued to receive octreotide treatment for a maximum of 12 total treatment cycles. Patients with stable disease at the end of two cycles remained on study but also were to receive prednisone at a dose of 0.6 mg/kg per day. Patients continued to receive octreotide plus prednisone for a total of 12 cycles unless undue toxicity or tumor progression occurred. Patients with progressive disease were removed from the study and treated at the investigator's discretion. No dose modifications of octreotide were permitted.

Every course of induction therapy was given on schedule regardless of the degree of myelosuppression. Patients with serious infection believed to be secondary to immunosuppression from prednisone were removed from the study.

Complete response was defined as complete disappearance of all but clinically detectable disease lasting for at least 4 weeks. Partial response was defined as $\geq 50\%$ decrease in the sum of bidimensional measurements lasting for at least 4 weeks without increase in size of known malignant disease. Stable disease was defined as less than a 50% decrease in the tumor size and no greater than a 25% increase in tumor size for at least 4 weeks. Progressive disease was defined as 25% or greater increase in the size of lesions or the appearance of metastatic lesions. Progression-free survival was measured from the time of first day of treatment until progression, and overall survival was measured until the date of death or date last seen alive.

For statistical considerations and study design, the primary end point was objective response. A total of 38 patients (34 assessable patients) were needed for a two-stage design. In the first stage, 17 eligible patients were to be enrolled. If three or more responses were observed, the design called for an additional 17 eligible patients to be accrued. The probability that octreotide would be declared inactive after the first stage was nearly 77% if the drug had little or no activity, whereas the probability of early stopping was less than 8% if the drug was active (true response rate, $\geq 30\%$). Similarly, the overall probability of rejecting octreotide was more than 91% if it was inactive, whereas there was at most a 9% chance of rejecting the drug if it was active.

Descriptive statistics were used to characterize patients at study entry. The method of Kaplan and Meier was used to describe progression-free survival and overall survival [10].

RESULTS

From April 1998 through November 2000, 42 patients with advanced thymoma or thymic carcinoma were entered onto the trial. Four patients were deemed ineligible because histology was inconclusive ($n = 1$), or the octreotide scan was not positive in any area of the body ($n = 2$) or not positive in the site of measurable disease ($n = 1$).

Patient Characteristics

Patient characteristics are listed in Table 1. Median age of all patients was 51.3 years (range, 31 to 71.5 years). There were an equal number of male and female patients. Seventy-nine percent of the patients were white. More than 60% of the patients had an ECOG performance status of 0. Thirty-two of the 38 patients had thymoma; six patients had thymic carcinoma or carcinoid. Thirty-five patients

Table 1. Patient Characteristics

Characteristic	No. of Patients	%
Age, years		
Median	51.3	
Range	31–71.5	
Sex		
Male	19	
Female	19	
Race or ethnicity		
White	30	79
Black	4	11
Hispanic	1	3
Asian	1	3
Native American	1	3
Other	1	3
Performance status		
0	24	63
1	14	37
Histology		
Thymoma	32	84
Thymic carcinoma	5	13
Thymic carcinoid	1	3
Previous surgery		
Biopsy only	5	13
Resection	30	79
None	3	8
Previous radiation therapy		
Primary only	21	55
Metastatic site only	6	16
Both metastatic and primary	5	13
None	6	16
Prior chemotherapy		
No. of prior regimens		
None	7	
1*	15	
2*	10	
>2*	8	
Type		
Cisplatin based	29	
Carboplatin based	4	
Nonplatinum	3	
Stage, Masaoka [32]		
III	2	5
IV	34	89
Incomplete data	2	5
Metastatic sites		
Pleura	23	61
Lung	22	58
Liver	7	18
Bone marrow	2	5
Bone	2	5
Subcutaneous	3	8
Other	11	29
Weight loss in previous 6 months		
None	25	66
< 5% of body weight	9	24
5%-10% of body weight	2	5
> 10% of body weight	1	3
Prior paraneoplastic syndrome		
Yes	3	8
No	35	97

*Some patients received both cisplatin and carboplatin-based chemotherapy.

(92%) had prior surgery, whereas 32 patients (84%) had prior radiation therapy and 31 patients (82%) had prior systemic chemotherapy.

Table 2. Toxicities, Grades 3, 4, and 5

	Grade (No. of patients)		
	3	4	5
Hematologic			
Anemia	2	1	—
Leukopenia	1	1	—
Thrombocytopenia	3	—	—
Infection without neutropenia	1	—	1
Weight gain	1	—	—
Diarrhea	3	—	—
Chemistries			
Bilirubin	—	1	—
Alkaline phosphatase	1	—	—
Aspartate aminotransferase	1	1	—
Alavine aminotransferase	—	1	—
Acidosis	—	1	—
Hyperglycemia	5	1	—
Hyperkalemia	1	—	—
Hypernatremia	1	—	—
Hypocalcemia	1	—	—
Creatinine	1	1	—
Fatigue	2	—	—
Anxiety or agitation	2	—	—
Depression 1	—	—	
Dyspnea	—	1	—
Other	—	3	1

The most common metastatic sites were the lung and pleura. Twenty-three patients had pleural metastases, seven patients had hepatic metastases, and four patients had locally advanced disease.

Toxicity

Grade 3 and 4 toxicity for patients treated with octreotide alone and those who were subsequently treated with octreotide plus prednisone are listed on Table 2. Eight patients had grade 4 or 5 toxicity. One patient treated with octreotide plus prednisone had a lethal toxicity secondary to a grade 5 infection without neutropenia. Three patients who had octreotide alone and four patients with octreotide plus prednisone had grade 4 toxicity consisting of acidosis, hyperglycemia, hypocalcemia, hypoglycemia, dyspnea, anemia, leukopenia, elevated bilirubin, AST or ALT, and elevated creatinine.

Response

In 38 assessable patients, there were two complete (5.3%) and 10 (25%) partial responses for an overall response rate of 30.3%. Fourteen patients (36.8%) had stable disease and 12 patients (31.6%) had progressive disease. Of 38 patients treated with octreotide alone, four patients (10.5%) had a partial response. Of 21 patients in whom prednisone was subsequently added, there were two complete and six partial responses. Therefore, overall two complete and 10 partial responses were observed for an overall objective response rate of 31.6% (95% CI, 17.5% to 48.7%).

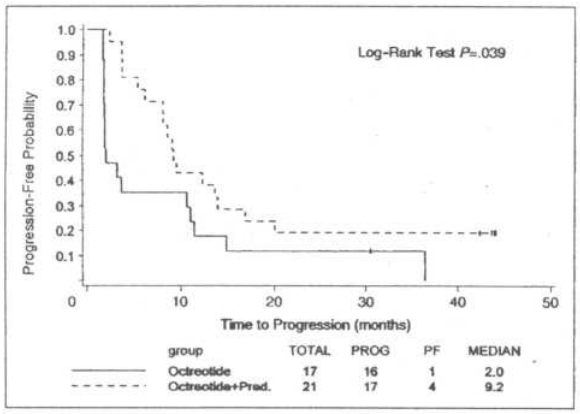

Fig 1. Progression-free survival. PROG, progression; PF, progression-free; Pred., prednisone.

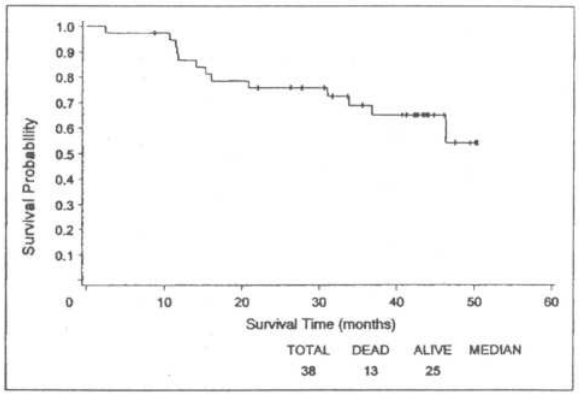

Fig 2. Overall survival.

Of note, none of the six patients with thymic carcinoid or carcinoma had an objective response to therapy.

Of the six patients with thymic carcinoma or carcinoid, two remain alive (27+ and 44+ months, respectively). The median time to progression in these six patients was 4.5 months (range of progression time, 1.8 to 9.5 months; one patient is still free of disease progression after 44 months). None had an objective response.

The progression-free survival is shown in Figure 1. As of August 9, 2003, a total of 33 patients (86.8%) have progressed, including 16 patients (94.1%) treated with octreotide alone and 17 patients (81.0%) treated with both octreotide and prednisone. As expected, the median progression-free survival for octreotide alone is shorter (2 months; 95% CI, 1.8 to 11.0 months) than that for patients treated with both octreotide and prednisone (9.2 months; 95% CI, 8.1 to 13.9 months). These differences are statistically significant ($P = .039$). The progression-free survival for patients with thymoma and thymic carcinoma was 8.8 months (95% CI, 3.7 to 12.3 months) and 4.5 months (95% CI, 1.9 to 9.5 months), respectively.

Twenty-five of 38 eligible patients (65.8%) are currently alive; the overall survival curve is shown in Figure 2. This includes nine patients (52.9%) treated with octreotide alone (95% CI, 27.8% to 77.0%); 16 patients (76.2%) treated with both octreotide and prednisone are alive (95% CI, 52.8% to 92.8%), as shown in Figure 3. The median survival time has not been reached for all patients (it has not been reached for thymoma, and is 23.4 months for thymic carcinoma). On the basis of Kaplan and Meier estimates, the 1- and 2-year survival rates were 86.6% and 75.7%, respectively. There were no differences in survival with respect to sex ($P = .388$) or race or ethnicity ($P = .576$); however, there was a significant difference in survival on the basis of performance status (Fig 4). Patients with ECOG performance status of 0 have significantly longer survival than those with a performance status of 1 ($P = .031$). The overall survival curves are shown for all patients in Figure 2 and are based on performance status in Figure 3.

DISCUSSION

Thymomas account for 40% of anterior mediastinal masses in adults. Histologically, thymomas are composed of epithelial cells (which are the putative source of malignancy), lymphocytes (both B and T cells), intradigitating reticulum cells, macrophages, and myoid cells [1]. Although neuroendocrine tumors of the thymus may occur, the most common tumors of the thymus are thymomas and thymic carcinomas [11]. As mentioned previously, surgical resection of early-stage thymoma is a standard approach. For those patients with advanced disease, combination chemotherapy alone or with additional local therapy (surgery or radiation therapy) is the treatment of choice. Combined-modality therapy has become the standard approach for

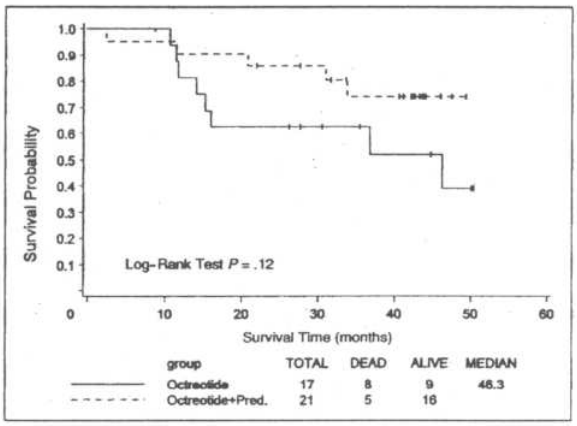

Fig 3. Overall survival by group. Pred., prednisone.

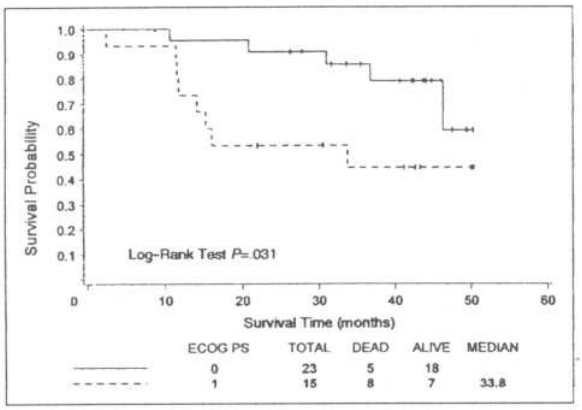

Fig 4. Overall survival by performance status. ECOG, Eastern Cooperative Oncology Group; PS, performance status.

patients with locally advanced disease [1,2,11]. In previously untreated patients, chemotherapy with PAC produces a 50% response rate in patients with advanced disease and a 70% response rate in patients with limited-stage thymoma [12,13]. As mentioned in various reviews, the addition of prednisone or vincristine may improve the response rate, but the overall survival of such patients did not seemed to be improved over that for PAC alone [1,2,11]. Approximately 50% to 70% of patients with locally advanced or metastatic thymoma will be candidates for second-line therapy.

SST is a naturally occurring peptide composed of 14 amino acids. SST receptors are present in a variety of tissues including the hypothalamus, cerebral cortex, gastrointestinal tract, and pancreas [14,15]. The SST receptors belong to a superfamily of G-protein–coupled receptors with several new transmembrane-spanning domains [14,15]. SST acts as a neurotransmitter in the CNS, which inhibits the release of various hormones such as growth hormone, glucagon insulin, and gastrin. In addition, SST has been demonstrated to have an antiproliferative effect in vitro in breast cancer cell lines, animal tumor models, and neuroendocrine tumors. The mechanism of the antiproliferative effect is uncertain, but inhibition of various hormone-releasing factors (including epidermal growth factor, transforming growth factor beta, growth hormone, and ILGF-1), modulation of immune activity, and inhibition of angiogenesis have all been postulated [16-21].

At least five structurally related membrane SST receptors ($SST_{1\ to\ 5}$) have been identified [33]. The most common SST receptor expressed in human tumors is the SST_2 subtype. These receptors are also found in different tissues in the body. SST receptors have been identified in a number of different malignancies. It should be noted that radionuclide octreotide scintography (which has greatest affinity for SST_2 and SST_5 receptors) has also demonstrated increased uptake in some autoimmune and infectious diseases such as sarcoidosis, Wegner granulomatosis, tuberculosis, and Graves disease [3,14,20]. Octreotide is a synthetic octapeptide SST analog that has a prolonged duration of effect compared with a naturally occurring SST. Octreotide binds with greater affinity to SST_2 and SST_5 receptors, with its greatest antiproliferative effects on tumors with SST_2 overexpression. The inhibition of tumor growth by octreotide and other SST analogs has been seen in a variety of tumors including cancer cell lines from breast, stomach, pancreas, lung, cervical, colorectal, and prostate cancers [21].

The therapeutic role of SST analogs in malignant tumors in vivo has been unclear. Several experimental tumors such as pancreas, renal cell, and human glioblastoma demonstrate growth inhibition by SST analogs [22-24]. Khanna et al [25] evaluated carboplatin plus octreotide or placebo in 44 assessable dogs and could not find any differences in the impact of tumor growth, but octreotide did demonstrate a 43% decrease in serum ILGF levels, but no differences in tumor ILGF mRNA was observed. In clinical trials octreotide did not have a favorable influence when compared with chemotherapy alone in patients with advanced adenocarcinoma of the pancreas [26,27]. In a patient with cholangiocarcinoma, a complete response was noted with octreotide. This seems to validate the in vitro data, with growth inhibition in the biliary tract cancer cells that are SSI-positive [28]. A prospective trial that examined long-acting octreotide plus tamoxifen failed to show an advantage compared with tamoxifen alone in patients with metastatic breast cancer [29].

Two patients with thymoma treated with octreotide plus prednisone have been reported. In both reports, tumor demonstrated positive uptake with indium-111 octreotide scintography [9,30]. The first published report by Palmieri et al [9] included a heavily pretreated patient with thymoma and pure red cell aplasia. The patient achieved a complete remission of the thymoma as well as resolution of the pure red cell aplasia. A partial response was also noted in a previously treated patient reported by Lin et al [30].

One of the difficulties interpreting the above-mentioned reports was the determination of the contribution of octreotide. Given that prednisone is a lympholytic agent, a reduction of the size of the tumor may not represent single-agent activity for octreotide. An increase in the response rates with cisplatin-based chemotherapy plus prednisone has been reported by some authors, but the influence on overall survival is unclear [11,31]. The current trial was developed to evaluate the role, if any, for octreotide alone. Indeed, a 10.5% objective response rate was observed for patients treated with octreotide without prednisone. It is noted that some of the patients who exhibited a minor response at 2 months did not receive prednisone per protocol but demonstrated an objective response with octreotide later.

Only five patients with thymic carcinoma were entered onto this trial and none of them responded. The ECOG has routinely treated thymic carcinoma in prospective trials of thymic malignancies. The small number of patients with thymic carcinoma does not allow any major treatment distinctions regarding thymoma. The role of octreotide on the immune system also deserves additional evaluation. Although not part of this study, it was noted that several of the patients with myasthenia gravis and pure red cell aplasia have had improvement of symptoms with octreotide.

There are several limitations of this trial. This trial does confirm modest activity of the long-acting SST analog in thymoma. The vast majority of the patients had at least one prior systemic regimen. Given that some of the objective responses occurred after the initial two cycles of therapy, it is possible that some of the remaining responding patients may have responded to octreotide alone without the addition of prednisone. In retrospect, the trial design would have more clearly defined the activity of octreotide had prednisone been added only once tumor progression occurred after the administration of octreotide.

The optimal dosage and schedule of octreotide for thymic malignancies remain uncertain. At the onset of this trial, sustained-release octreotide was not yet commercially available in this country. The current recommended starting dose for octreotide long-acting release is 20 to 30 mg/mo. This represents a comparable daily dose of approximately 150 to 300 μg tid, which is much lower than the dose used in this study. Anecdotally, one patient who had stable disease while receiving therapy was changed to the long-acting release formulation after about 1 year. She later experienced disease progression but again stabilized after retreatment with short-acting octreotide. The mechanism of action for cytotoxicity of octreotide also remains uncertain. Only those patients with positive uptake on octreotide scintography were eligible. Octreotide may exhibit cytotoxic activity on the basis of direct or indirect effects on ILGF-1, angiogenesis, or other mechanisms [16-18,30].

In summary, octreotide alone and with the addition of prednisone is capable of producing objective responses in selected patients with thymoma. Additional studies of this drug (including long-acting octreotide) in patients with thymic malignancies and paraneoplastic syndrome associated with thymoma are warranted. The modest activity of octreotide leads us to believe it should be part of treatment considerations in the patients who experience disease relapse. The role of short-acting octreotide in earlier therapy and that of long-acting octreotide in patients with advanced thymoma remains to be discerned.

Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

REFERENCES

1. Cameron RB, Loehrer PJ, Thomas CR Jr: Neoplasms of the mediastinum, in DeVita VT, Hellman S, Rosenberg SA (eds): Cancer: Principles and Practice of Oncology (ed 6). Philadelphia, PA, Lippincott-Raven, 2001, pp 1019-1036
2. Thomas CR, Wright CD, Loehrer PJ: Thymoma: State of the art. J Clin Oncol 17:2280-2289, 1999
3. Krenning EP, Kwekkeboom DJ, Bakker WH, et al: Somatostatin receptor scintography with [^{111}In-DTPA-D-Phe^1]-and [^{123}I-Tyr^3]-octreotide: The Rotterdam experience with more than 1000 patients. Eur J Nucl Med 20:716-731, 1993
4. Lastoria S, Vergara E, Palmieri G, et al: In vivo detection of malignant thymic masses by indium-111-DTPA-D-Phe^1-octreotide scintigraphy. J Nucl Med 39:634-639, 1998
5. Ferone D, van Hagen PM, van Koetsveld PM, et al: In vitro characterization of somatostatin receptors in the human thymus and effects of somatostatin and octreotide on cultured thymic epithelial cells. Endocrinology 140:373-380, 1999
6. Fuller PJ, Verity K: Somatostatin gene expression in the thymus gland. J Immunol 143:1015-1017, 1989
7. Timsit J, Savino W, Safieh B, et al: Growth hormone and insulin-like growth factor-1 stimulate hormonal function and proliferation of thymic epithelial cells. J Clin Endocrinol Metab 75:183-188, 1992
8. Andersen A, Pedersen H, Bendtzen K, et al: Effects of growth factors on cytokine production in serum-free cultures of human thymic epithelial cells. Scand J Immunol 38:233-238, 1993
9. Palmieri G, Lastoria S, Colao A, et al: Successful treatment of a patient with a thymoma and pure red cell aplasia with octreotide plus prednisone. N Engl J Med 336:263-265, 1997
10. Kaplan EL, Meier P: Nonparametric estimation from incomplete observations. J Am Stat Assoc 53:457-481, 1958
11. Loehrer PJ, Wick MR: Thymic malignancies, in Ettinger D (ed): Thoracic Oncology. Norwell, MA, Kluwer, 2001, pp 277-302
12. Loehrer PJ, Chen M, Kim KM, et al: Cisplatin, doxorubicin and cyclophosphamide plus radiation therapy for limited stage, unresectable thymoma: An intergroup trial. J Clin Oncol 15: 3093-3099, 1997
13. Loehrer PJ, Kim K, Aisner SC, et al: Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: Final results of an intergroup trial. J Clin Oncol 12:1164-1168, 1994
14. Bruns C, Stolz B, Raulf F, et al: Somatostatin receptor expression: Therapeutic considerations. J Endocrinol Invest 20:2-4, 1997
15. Reisine T, Bell GI: Molecular biology of somatostatin receptors. Endocr Rev 16:427-442, 1995
16. Rauly I, Saint LN, Delesque N, et al: Induction of a negative autocrine loop by expression of SST2 somatostatin receptor in NIH 3T3 cells. J Clin Invest 97:1874-1883, 1996
17. Delesque N, Buscail L, Esteve JP, et al: A tyrosine phosphatase is associated with the somatostatin receptor. Ciba Found Symp 190:187-196, 1995
18. Buscail L, Esteve JP, Saint LN, et al: Inhibition of cell proliferation by the somatostatin analogue RC-160 is mediated by somatostatin receptor subtypes SSTR2 and SSTR5 through difference mechanisms. Proc Natl Acad Sci U S A 92:1580-1584, 1995
19. Buscail L, Delesque N, Esteve JP, et al: Stimulation of tyrosine phosphatase and inhibition of cell proliferation by somatostatin analogs: Mediation by human somatostatin receptor subtypes SSTR1 and SSTR2. Proc Natl Acad Sci U S A 91:2315-2319, 1994
20. Reubi JC, Schaer JC, Laissue JA, et al: Somatostatin receptors and their subtypes in human tumors and in peritumoral vessels. Metabolism 45:39-41, 1996
21. Weckbecker G, Raulf F, Stolz, ••• et al: Somatostatin analogs for diagnosis and treatment of cancer. Pharmacol Ther 60:245-264, 1993
22. Szepeshazi K, Schally AV, Halmos G, et al: Targeting of cytotoxic somatostatin analog AN-238 to somatostatin receptor subtypes 5 and/or 3 in experimental pancreatic cancers. Clin Cancer Res 7:2854-2861, 2001

23. Plonowski A, Schally AV, Nagy A, et al: Inhibition of metastatic renal cell carcinomas expressing somatostatin receptors by a targeted cytotoxic analogue of somatostatin AN-238. Cancer Res 60:2996-3001, 2000

24. Kiaris H, Schally AV, Nagy A, et al: Regression of U-87 MG human glioblastomas in nude mice after treatment with a cytotoxic somatostatin analog AN-238. Clin Cancer Res 6:709-717, 2000

25. Khanna C, Prehn J, Hayden D, et al: A randomized controlled trial of octreotide pamoate long-acting release and carboplatin versus carboplatin alone in dogs with naturally occurring osteosarcoma: Evaluation of insulin-like growth factor suppression and chemotherapy. Clin Cancer Res 8:2406-2412, 2002

26. Burch PA, Block M, Schroeder G, et al: Phase III evaluation of octreotide versus chemotherapy with 5-fluorouracil or 5-fluorouracil plus leucovorin in advanced exocrine pancreatic cancer: A North Central Cancer Treatment Group Study. Clin Cancer Res 6:3486-3492, 2000

27. Sulkowski U, Buchler M, Pederzoli P, et al: A phase II study of high dose octreotide in patients with unresectable pancreatic carcinoma. Eur J Cancer 35:1805-1808, 1999

28. Tan CK, Podila PV, Taylor JE, et al: Human cholangiocarcinomas express somatostatin receptors and respond to somatostatin with growth inhibition. Gastroenterology 108:1908-1916, 1995

29. Bajetta E, Procopio G, Ferrari L, et al: A randomized multicenter prospective trial assessing long-acting release octreotide pamoate plus tamoxifen as first line therapy for advanced breast cancer carcinoma. Cancer 94:299-304, 2002

30. Lin K, Nguyen BD, Ettinger DS, et al: Somatostatin receptor scintigraphy and somatostatin therapy in the evaluation and treatment of malignant thymoma. Clin Nucl Med 24:24-28, 1999

31. Shin DM, Walsh GL, Komaki R, et al: Induction chemotherapy followed by surgical resection, radiotherapy, and consolidative chemotherapy may cure the advanced stages of unresectable invasive thymoma. Ann Intern Med 129:100-104, 1998

32. Masaoka A, Monden Y, Nakahaka K, et al: Follow up study of thymoma with special reference to their clinical stages. Cancer 48:2485-2492, 1981

33. Reubi JC, Scar JC, Waser B, et al: Affinity profiles for human somatostatin receptor subtypes SST1-SST5 of somatostatin radiotracers selected for scintigraphic and radiotherapeutic use. Eur J Nucl Med 27:273-282, 2000