The British Journal of Radiology, 84 (2011), e7–e10

CASE REPORT

The role of somatostatin analogues in the treatment of advanced malignant thymomas: case report and review of the literature

L PETTIT, MRCP and A EL-MODIR, FRCR

SpR Clinical Oncology, University Hospital Birmingham, Edgbaston, Birmingham, UK

ABSTRACT. Thymomas are the most common tumours of the anterior mediastinum; their clinical course is often complicated by accompanying autoimmune and paraneoplastic syndromes. Advanced malignant thymoma is particularly challenging to manage owing to the lack of evidence from randomised trials to guide treatment. Combination first-line chemotherapy has been trialled in several small studies and has been reported to produce a 50–80% response with platinum-containing regimes. Progression following first-line chemotherapy is difficult to manage as most of these patients maintain a good performance status and demand further active palliative treatment. There is no standard second-line treatment. We report a good clinical and radiological response to third-line palliative octreotide therapy in a patient who had a positive octreotide scan.

Received 9 October 2009
Revised 12 January 2010
Accepted 27 January 2010

DOI: 10.1259/bjr/16436465

Thymomas are the most common tumours of the anterior mediastinum, tending to present in the fourth or fifth decades of life, although they have been reported in any age group [1]. There is no clear gender preponderance. Histologically they are epithelial tumours associated with a lymphoid component and tend to be slow growing. The majority of patients will have an encapsulated or non-invasive tumour that can usually be cured by surgical resection; distant metastases are uncommon at presentation. However, around one-third of patients will develop locally advanced or metastatic disease, warranting additional therapy [2].

Management of advanced malignant thymoma is a particularly challenging field owing to the lack of evidence from randomised trials to guide treatment. The treatment strategy depends on the clinical stages of thymoma, which is usually based on the Masoka classification [3].

All suitable patients should undergo surgery. For patients who present with advanced inoperable disease or following recurrence after surgery, guidelines are scarce. Once standard first-line chemotherapy has been tried, management becomes more challenging, especially as accompanying autoimmune and paraneoplastic syndromes often complicate management. Myasthaenia gravis has been reported in up to 30% of cases. Table 1 illustrates other paraneoplastic diseases associated with thymomas [1].

Thymomas exhibit unique biology. The thymus is a primary lymphoid organ that plays a role in regulating the proliferation and differentiation of T cells. This is controlled by cytokines and thymic hormones produced by the thymic stroma. Neuroendocrine hormones can influence these thymic epithelial cells. Somatostatin, a naturally occurring peptide, is among them, but its complete effects have yet to be fully identified [4]. Somatostatin receptors have been identified in both normal tissues and tumour cells. Octreotide, a somatostatin analogue, binds with high affinity to some subtypes of the somatostatin receptor. Octreotide scans visualize somatostatin receptors in various human neoplasms *in vivo*. This can be helpful in assessing primary and recurrent malignant thymomas to define the extent of disease and receptor status. The presence of somatostatin receptors provides the rationale for the use of a treatment based on the octreotide analogue. For non-thymoma tumours, it has been noted that a positive scan predicts a good response to treatment with octreotide [4].

A small phase II study by Palmieri et al [5] enrolled 16 patients with advanced or recurrent thymic tumours who had progressed following conventional palliative chemotherapy. Patients who had previously had surgery or radiotherapy were not excluded. All patients needed to have a high uptake on somatostatin receptor scintigraphy with ^{111}In-[DTPA-D-Phe1] (octreotide scan). Patients were

Table 1. Paraneoplastic syndromes associated with thymoma

Acute pericarditis	Pernicious anaemia
Addison's disease	Pitiriasis rubra pilaris
Agranulocytosis	Polymyositis
Alopecia areata	Red blood cell aplasia
Cushing's syndrome	Rheumatoid arthritis
Haemolytic anaemia	Sarcoidosis
Hypogammaglobulinaemia	Scleroderma
Limbic encephalopathy	Sensorimotor radiculopathy
Myasthaenia gravis	Stiff-person syndrome
Myocarditis	Systemic lupus erythmatosus
Nephrotic syndrome	Thyroiditis
Panhypopituitarism	Ulcerative colitis

Address correspondence to: Laura Pettit, SpR Clinical Oncology, University Hospital Birmingham, Edgbaston, Birmingham B15 2TU. E-mail: laura.pettit@uhb.nhs.uk

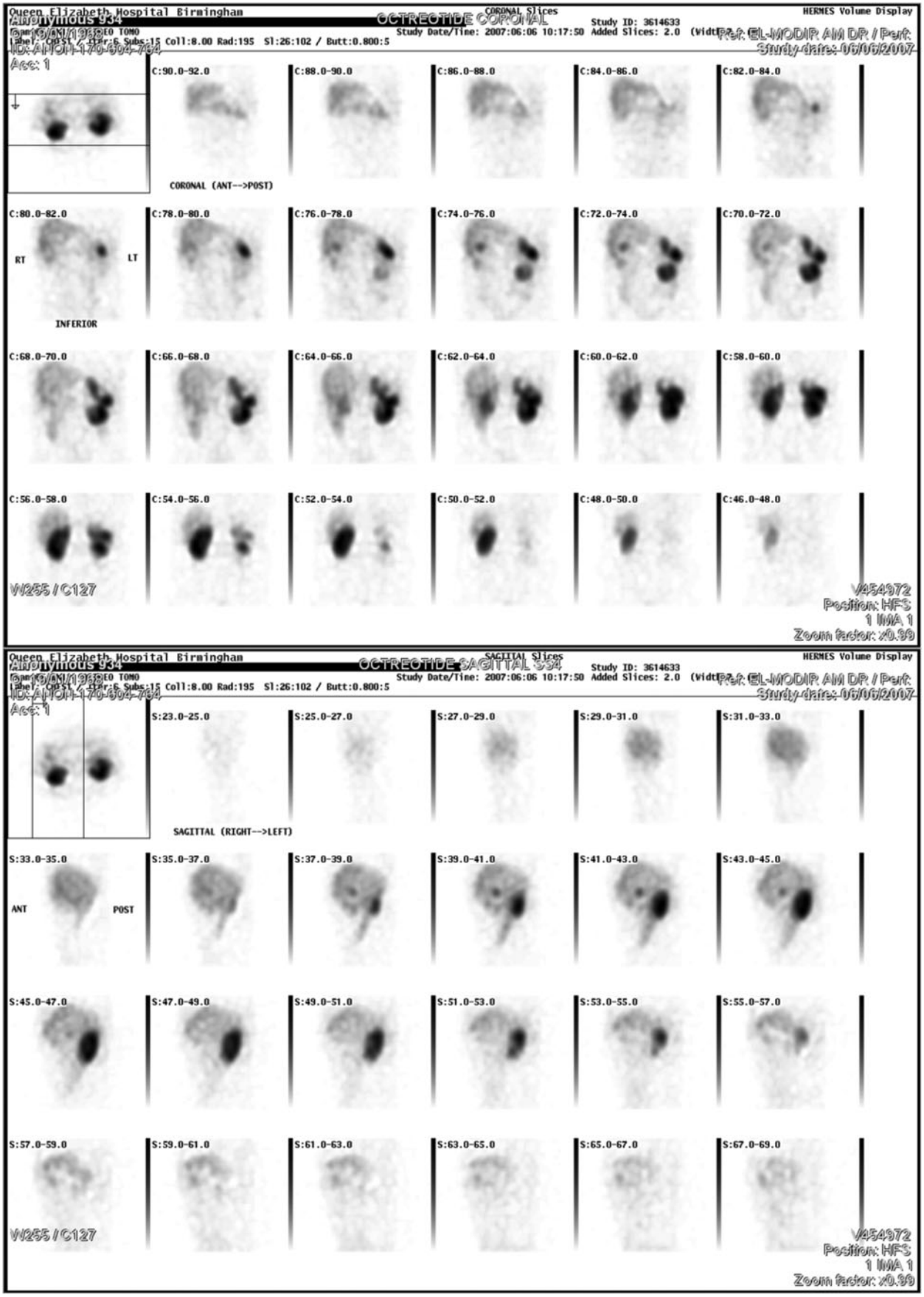

Figure 1. Octreotide scan (June 2007).

given the somatostatin analogue octreotide subcutaneously along with prednisolone orally (doses were 0.6 mg kg^{-1} day^{-1} for 3 months, then 0.2 mg kg^{-1} day^{-1} for follow up). The overall response rate was 37%. This included one complete response (6%), 5 partial responses (31%), 6 patients with stabilisation of disease and 4 patients who progressed on treatment. Median survival was 15 months and the median time to progression was 14 months. Overall, treatment was well tolerated [5].

We report a case where octreotide was used successfully in the third-line setting in advanced malignant thymoma.

Case presentation

We report the case of a 37-year-old man of Indian ethnicity who initially presented with myasthaenia gravis in 1989. He underwent a thymectomy and was found to have a stage II malignant thymoma. The tumour was fully excised and he did not receive adjuvant radiotherapy.

In March 2005, he relapsed with inoperable disease in the left hemithorax complicated by nephrotic syndrome. He received six cycles of first-line palliative chemotherapy using a combination of epirubicin, cyclophosphamide and carboplatin, between June and October 2005. He achieved a good partial radiological response but his disease was still inoperable. He remained well and asymptomatic until February 2006 when progression was noted within the left hemithorax. He went on to receive second-line palliative chemotherapy with six cycles of the VIP (etoposide, ifosphomide, cisplatin) regime, etoposide, ifosphomide and cisplatin, between March 2006 and July 2006. Again, he achieved a good partial response and remained progression free until April 2007, when he became symptomatic with increasing shortness of breath and chest pain. A repeat CT thorax revealed progressive disease.

Based on evidence from the Phase II trial by Palmieri [5], an octreotide scan was performed, which revealed an increased uptake in the left hemithorax, spleen and in the right lobe of the liver (Figure 1). We initiated treatment with octreotide 50 mg three times daily in April 2007 (subsequently increasing to 200 mg three times daily) and prednisolone 15 mg once daily. He tolerated treatment well, with significant improvement of his chest symptoms. In September 2007, octreotide was converted to Sandostatin long-acting release (LAR) 30 mg im. The response on CT scan is illustrated in Figure 2 (before Sandostatin treatment) and Figure 3 (after Sandostatin treatment).

In October 2008 he was admitted to hospital with bradycardia requiring a pacemaker (visible on CT scan of the thorax in Figure 3). This was thought to be related to autonomic dysfunction, which could be another autoimmune manifestation of thymomas. Interestingly his nephrotic syndrome in 2005 was due to minimal change glomerular nephropathy and he also developed pitiriasis rubra pilaris during the course of his illness. These are all known associations with thymomas (see Table 1 for full list).

Treatment continues with Sandostatin. Duration of treatment with a somatostatin analogue currently stands at 30 months. He remains alive and independent with radiological evidence of response at the time of submission of this report.

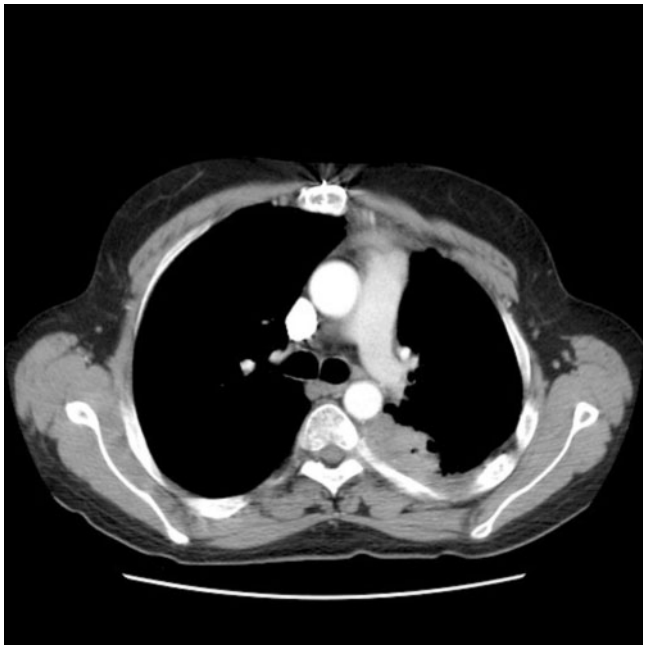

Figure 2. CT scan before Sandostatin (April 2007).

Discussion

Advanced malignant thymomas remain a challenge to treat owing to the lack of guidelines or randomised clinical trials. Combination first-line chemotherapy has been trialled in several small studies and has been reported to produce a 50–80% response rate [6]. These studies are summarised in the Table 2 [7].

Progression following first-line chemotherapy is difficult to manage as most of these patients maintain a good performance status and demand further active palliative treatment. The rationale for octreotide therapy came from a small phase II study by Palmieri et al [5], as previously discussed, giving an overall response rate of 37%, including one complete response (6%).

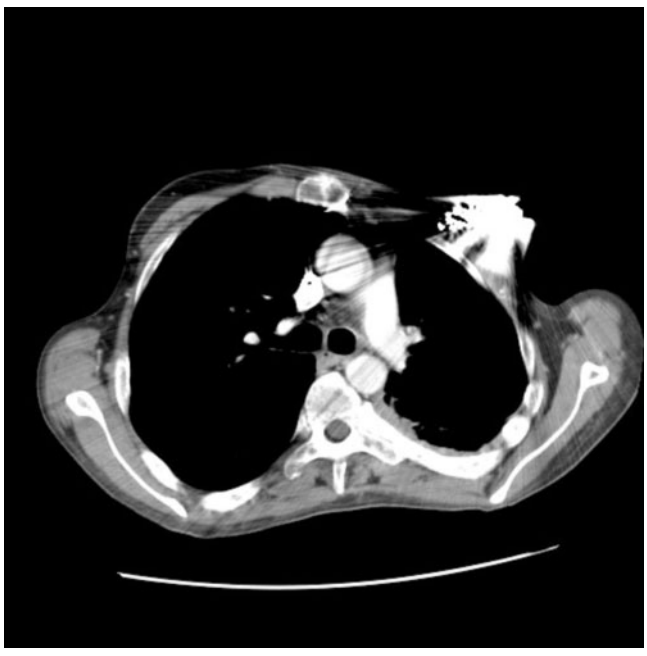

Figure 3. CT scan after Sandostatin (October 2008).

Table 2. Results of combination chemotherapy with and without radiation therapy or surgery for invasive thymoma [6]

Study	No. of patients	Chemotherapy regime	Surgery	Radiation	PR/CR	Path CR	Survival
Fornsero et al, [12] 1991	37	Doxyrubicin Cisplatin Vincristine Cyclophosphamide	10/16		16 CR 18 PR	7/10	15 months median
Giaccone et al, [7] 2006	16	Cisplatin Etoposide			5 CR (31%) 4 PR (25%)		4.3 years medium
Loehrer et al, [10] 2001	28	Cisplatin Etoposide Ifosphomide			9 PR (32%)		32 months median, 70% 2 years
Loehrer et al, [11] 1994	30	Doxyrubicin Cisplatin Cyclophosphamide			3 CR (10%) 12 PR (40%)		38 months median, 32% 5 years
Oshita et al, [9] 1995	14	Cisplatin Cyclophosphamide Doxyrubicin Etoposide	2	7	6 PR		14.7 months median
Chemotherapy only: pooled results	74	Above regimes including Cisplatin Etoposide Ifosphomide Doxorubicin Cyclophosphamide			CR (10%) PR (34%)		

Interestingly, glucocorticoid receptors have been identified in thymic epithelial cells [8]; they have been shown to modulate thymic epithelial cell proliferation and production of thymic hormones. Therefore, corticosteroids is a treatment option that been shown to induce tumour regression as a monotherapy [8].

Somatostatin has also been shown to inhibit the growth of tumour cells by inhibiting angiogenesis and growth factors such as insulin-like growth factor (IGF)-1. Low-dose steroids have also been postulated to enhance the expression of the somatostatin gene in the thymic gland. The combination of somatostatin analogues and steroids appears to have a synergistic effect inducing a higher response rate.

Malignant thymoma is a rare tumour. In patients with advanced or recurrent disease, platinum-based palliative chemotherapy is the gold standard with response rates between 50% and 80%. There is no standard second-line treatment. We have reported a good clinical and radiological response to third-line palliative octreotide therapy in a patient who had a positive octreotide scan. Randomised clinical trials are the ultimate goal.

References

1. Thomas CR, Wright CD, Loehrer PJ. Thymoma: state of the art. J Clin Oncol 1999;17:2280–9.
2. Loehrer PJ, Chen M, Kim K, Aisner SC, Einhorn LH, Livingston R, et al. Cisplatin, doxorubicin, and cyclophosphamide plus thoracic radiation therapy for limited-stage unresectable Thymoma: An Intergroup Trial. J Clin Oncol 1997;15:3093–9.
3. Masaoka A, Monden Y, Nakahara K Tanioka T. Follow-up study of thymomas with special reference to their clinical stages. Cancer 1981;48:2485–92.
4. Ferone D, van Hagen MP, Kwekkeboom DJ, van Koetsveld PM, Moony DM, Lichtenauer-Kaligis E, et al. Somatostatin Receptor Subtypes in Human Thymoma and Inhibition of Cell proliferation by Octreotide in Vitro. J Clin Endocrinol Metab 2000;85:1719–26.
5. Palmieri G, Montella L, Martignetti A, Muto P, Di Vizio D, De Chiara A, et al. Somatostatin analogs and prednisone in advanced refractory thymic tumors. Cancer 2002;94: 1414–20.
6. Eng TY, Scarbrough TJ, Thomas CR. Mediastinum and trachea. Principles and practices of radiation oncology Philadelphia Lippincott Williams and Wilkins (4th edn). 1244–57.
7. Giaccone G. Systemic treatment of malignant thymoma. Curr Opin Oncol 2005;17:140–6.
8. Palmieri G, Montella L, Lastoria S. Thymoma and somatostatin analogs. Biology, diagnostic and clinical practice. Minerva Endocrinol 2001;26:193–5.
9. Oshita F, Kasia T, Kurata T, Fukuda M, Yamamoto N, Ohe Y, et al. Intensive chemotherapy with cisplatin, doxorubicin, cyclophosphamide, etoposide and granulocyte colony-stimulating factor for advanced thymoma or thymic cancer: preliminary results. Jpn J Clin. Oncol. (1995);25 (5):208–212.
10. Loehrer PJ, Kim K, Aisner SC, Livingston R, Einhorn LH, Johnson D et al. For the Eastern Cooperative Oncology Group, Southwest Oncology Group, Southeastern Cancer Study Group. Cisplatin plus doxorubicin plus cyclophosphamide in metastatic or recurrent thymoma: final results of an intergroup trial. J Clin Oncol 1994;12:1164–8.
11. Loehrer PJ, Jiroutek M, Aisner S, Aisner J, Green M, Thomas CR, et al. Combined etoposide, ifosfamide, and cisplatin in the treatment of patients with advanced thymoma and thymic carcinoma: an intergroup trial. American Cancer Society 2001;91:2010–5.
12. Fornasiero A, Daniele O, Ghitto C, Fiorentino MV, Piazza M, Fione-Donali L, et al. Chemotherapy for invasive thymoma. A 13-year experience. Cancer 1991;68:30–33.