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European Journal of Cardio-thoracic Surgery 21 (2002) 913–917

EUROPEAN JOURNAL OF CARDIO-THORACIC SURGERY

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Long-term survival of atypical bronchial carcinoids with liver metastases, treated with octreotide ☆

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Received 14 September 2001; received in revised form 8 January 2002; accepted 16 January 2002

Abstract

Objective: To demonstrate that liver metastases by radically resected atypical carcinoids of the lung can be effectively treated by new somatostatin analogs. **Methods**: Between January 1977 and December 1999, 126 patients affected by bronchial carcinoids were submitted to a radical resection of the lung. Seven of them (5.5%) presented liver metastases 27, 22, 14, 18, 16, 12 and 9 months after surgery: carcinoid syndrome (CS) was ever present. ^{111}In–DTPA–pentetreotide scintigraphy (Octreoscan) and ultrasound guided biopsy were performed in all cases, and the presence of somatostatin receptors sst_2 was demonstrated by polymerase chain reaction (PCR) method. **Results**: Five patients refused the proposed chemotherapy, and liver alcoholization was not feasible. Octreotide was administered at the dose of 1500 μg/daily subcutaneously. CS was controlled and also high urinary 5-hydroxyindoleacetic acid values returned to normal after a median of 7 days (range 4–10 days) of medical treatment. No important side effects were registered, and a good quality of life was observed. The patients are alive and well at 51, 36, 24, 24, 23, 19, and 16 months after the diagnosis of the metastases, respectively. In two cases ultrasounds revealed the reduction and in one case the complete resolution of the liver lesion. **Conclusions**: Octreotide is effective in controlling symptoms of CS of patients with liver metastases of resected atypical bronchial carcinoid. The efficacy of the drug is due to the presence of sst_2 somatostatin receptors in the pathologic tissue, as demonstrated by PCR method. The positivity to Octreoscan depends on the presence of the same receptors. Octreoscan may be used in the follow-up of these neuroendocrine neoplasms of the lung. A positivity to Octreoscan is predictive for an effective therapy with octreotide.

Keywords: Lung; Neuroendocrine tumors; Liver metastases; Octreotide; Scintigraphy; Survival

1. Introduction

Bronchial carcinoids (BC) are rare tumors: less than 2% of all pulmonary neoplasm are carcinoid [1], 90% of them are confined to the bronchus and only 10% demonstrate regional lymph node involvement. The recent classification of lung tumors by the World Health Organization (WHO) and International Association for the Study of Lung Cancer (IASLC) consider BC as part of the neuroendocrine tumor spectrum (typical carcinoid, atypical carcinoid, large cell neuroendocrine carcinoma and small cell carcinoma), and typical and atypical carcinoids are grouped together [2].

Neuroendocrine tumors (NT) of the lung are derived from the Kulchitsky cell, which belongs to the amine precursor uptake and decarboxylation (APUD) system. Carcinoid, like small cell lung cancer, may secrete hormones, such as ACTH or arginine vasopressin and thus cause paraneoplastic syndromes, which resolve with their resection [3].

In addition, metastatic NT (usually in the liver) may produce the carcinoid syndrome (CS), characterized by cutaneous flushing, bronchoconstriction, diarrhoea and cardiac valvular lesions, which small cell lung cancer does not.

Atypical carcinoids seem to be more aggressive than typical ones: atypical carcinoids metastatize in 70% of the cases to regional lymph-nodes, or liver, bone or brain, when the metastatic rate of typical carcinoids is only of about 5%.

We report our experience about metastatic (liver) atypical carcinoids of the lung with CS, in which medical therapy with octreotide was effective in controlling CS and in prolonging the patients' survival. No important side effects were observed, while a good quality of life was guaranteed to all patients.

We also suggest the use of ^{111}In–DTPA–pentetreotide scintigraphy (Octreoscan) in the preoperative study and in the follow-up of patients with neuroendocrine tumors of the lung.

☆ Presented at the joint 15th Annual Meeting of the European Association for Cardio-thoracic Surgery and the 9th Annual Meeting of the European Soceity of Thoracic Surgeons, Lisbon, Portugal, September 16–19, 2001.

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1010-7940/02/$ - see front matter
PII: S1010-7940(02)00055-6

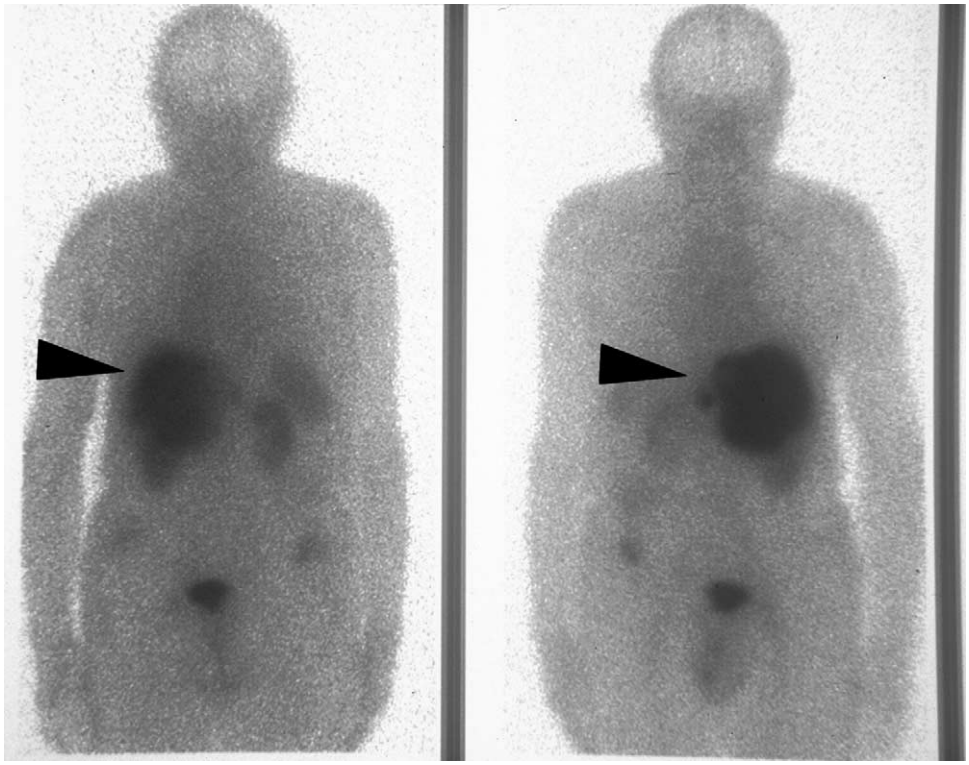

Fig. 1. ^{111}In–DTPA–pentetreotide whole body scintigraphy (Octreoscan) showing an elective uptake of the radiolabeled octreotide in the liver, expression of distant localization of the neuroendocrine tumor of the lung (arrow).

2. Material and methods

Between January 1977 and December 1999, at the Department of Thoracic Surgery of the University of Torino (Italy), 126 patients were submitted to a radical resection for bronchial carcinoid. The complete series is the object of another paper [4]. Seven out of these patients (5.5%), affected by T2N0 atypical carcinoid and operated on after January 1993, presented liver metastases 27, 22, 14, 18, 16, 12 and 9 months after the operation (two upper left lobectomies, three lower right lobectomies and two upper right lobectomies). They consisted of five males and two females; median age was 63.5 years (range 61–69 years). Distant localizations were discovered because of the appearance of CS.

Facial flushing, diarrhoea and systemic hypotension were the common symptoms at presentation. One patient developed asthma. One patient with a large liver metastasis developed several carcinoid crisis, with severe systemic hypertension, thoracic and facial flushing and diarrhoea.

High levels of urinary 5-hydroxyindoleacetic acid (5HIAA) were observed in all patients: median value was 86.3 mg/24 h (range 55–168.8) with normal values ranging from 2 to 10 mg/24 h.

Octreoscan was performed in all cases. Octreoscan was routinely used in our Department (in cooperation with the Service of Nuclear Medicine of the University of Torino) since July 1995; by this diagnostic procedure the metastases were detected in all the patients, but no other elective uptakes of the radiolabeled pentetreotide were shown (Figs. 1 and 2). Ultrasounds confirmed the scintigraphic data, and liver biopsy was carried out in all patients. Cytology and immunohistological examinations confirmed the neuroendocrine nature of the neoplastic cells, and the presence of somatostatin receptors was demonstrated by polymerase chain reaction (PCR) method.

Liver alcoholization was not feasible, because of the

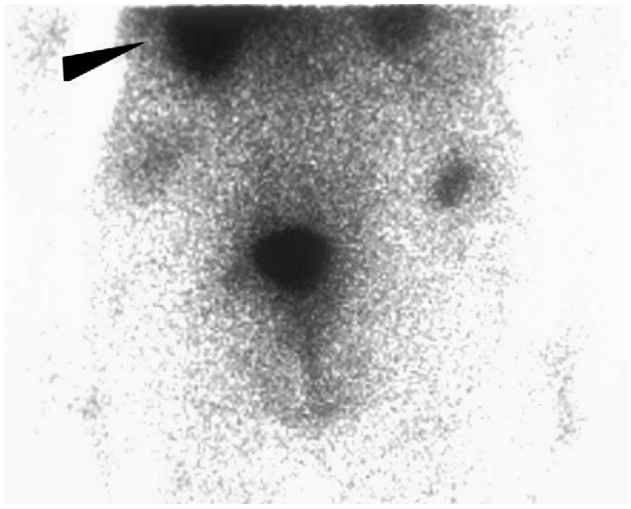

Fig. 2. Detail of the Octreoscan showing the liver metastase.

number, the site, the size and the localization of the metastases. Chemotherapy was proposed to five patients, but they refused it. Two patients had a poor performance status and chemotherapy was not considered in the therapeutic program.

Thus, all the patients received octreotide (Sandostatina Sandoz) at the dose of 1500 μg/daily subcutaneously.

3. Results

CS and carcinoid crisis were completely controlled. Urinary levels of 5HIAA were controlled every week during the first month of the treatment, and every month after; their values returned to normal after a median of 7 days (range 4–10 days).

The patients are alive and well 51, 36, 24, 24, 23, 19 and 16 months after the beginning of the medical treatment.

No important side effects were registered: gall-bladder lithyasis was observed in only three cases, systemic hypertension in two, well controlled with the common medical therapy, and good quality of life was observed in all patients.

Liver metastases were reduced to 60% of their volume in two cases (28.5%), and in one (14.2%) ultrasounds revealed the complete regression of the lesion 10 months after the beginning of the therapy. This patient continued the treatment 3 months after, and no other lesions were observed in the follow-up.

We compared the survival of these patients, with that of the two patients operated for atypical carcinoid, in the first period of our series, which developed liver metastases: both of them died in 13 and 10 months.

4. Discussion

BC are a rare entity: they represent no more than 2% of lung tumors [1].

Recent classification is based on the concept of the biological behavior of these tumors. As reported by many authors [5–10] atypical carcinoid has a more aggressive biological behavior than typical one. Recurrences are more frequent and generally related to the presence of hilar or mediastinal lymph-node metastases, while the size of the tumor is not predictive for recurrence or distant metastases.

NT of the lung express tissue receptors for somatostatin (sst_1–sst_5 subtype receptors), well detected by PCR technique.

These receptors are also expressed in recurrences or in their distant localizations [11,12]. The role of these receptors is to be elucidated, but the current generation of somatostatin analogs (octreotide, lanreotide) bind with high affinity to sst_2 receptor subtype, with low affinity to sst_3 and sst_5 and do not bind at all to sst_4 and sst_1 [13]. Thus, tissue expressing sst_2 receptors became a potential target for new somatostatin analogs.

In vivo expression of sst_2 receptors is provided by Octreoscan [9,10].

Octreoscan is effective in detecting the primary tumor at diagnosis, its increase in size and its local recurrence or distant metastases, in some cases before the appearance of symptoms [9,10].

Scintigraphy with radiolabeled octreotide was first used in 1991 in the staging of neuroendocrine tumors of the lung after chemo and radiotherapy [10]. Lamberts and co-workers [14] demonstrated the possibility of an early detection of asymptomatic brain and bone metastases in patients with small cell lung cancer, in whom traditional radiological procedures were negative, using octreoscan.

^{111}In–DTPA–Pentetreotide scintigraphy appears as a useful diagnostic tool for an accurate preoperative staging and for an early detection of local recurrences or metastases in neuroendocrine tumors of the lung, as we published in 1997 [10,15]. Octreoscan is also effective in the follow-up of these tumors.

Serotonin (5-hydroxytryptamine, 5HT) is the most common secretive product of neuroendocrine neoplasm [16,17]. These tumors synthesize the 5HT by enzymatic modification of circulating tryptophan. Serotonin induces intestinal secretion, stimulates intestinal motility and inhibits intestinal absorption. Thus high 5HT blood levels cause diarrhoea. Serotonin also stimulates fibroblast growth and fibrogenesis and thus it may mediate or accelerate the peritoneal and cardiac valvular fibrosis in CS [16,17].

5HT is metabolized in the blood to 5HIAA which is cleared by the kidneys. Measurement of urinary 5HIAA excretion is the most useful diagnostic test in CS [17].

Effective treatment of CS may require more than one approach: therapy should be selected in accordance with the severity of the symptoms. If metastatic disease is recognized, surgery is the therapy of choice, when possible; mild diarrhea can be treated with hypomotility drugs, and flushing, if rare and mild, may not require medical treatment. Hepatic resection or hepatic arterial embolization have been used in selected patients with a good performance status [18].

While in patients, in whom surgery or chemotherapy is not feasible, new antihormone drugs may be used to control CS [18].

The pharmacological management of CS includes drugs to inhibit synthesis, release or peripheral actions of the circulating tumor products. Chemotherapy with doxorubicin alone or streptozocin plus 5-FU achieves a response rate in 23–33% of cases [19]. Hepatic artery occlusion followed by sequential chemotherapy is effective in selected patients [19].

In patients with a mild syndrome, symptomatic treatment of diarrhea may be sufficient, while a more aggressive treatment with cytotoxic agents, interferon, somatostatin analogs may be indicated in patients with severe symptoms. Many authors [10,11,19–21] report the effectiveness of octreotide in the control of CS and in ameliorating symptoms. This antihormonal drug is well tolerated, without important side effects, and it appears as a significant advance in CS therapy.

The optimal dose of octreotide in long-term control of metastazing neuroendocrine carcinomas has not yet been established [21]. In literature there are many reports [21,22] of long-term survival of patients with malignant metastazing neuroendocrine (not only lung tumors) carcinomas treated with octreotide. Deguchi et al. [22] described the case of a patient with prolonged survival for 4.5 years with high dose octreotide therapy, with a survival of 7.5 years after the first flushing, in spite of severe carcinoid crisis. The author reported a dose escalation till 5.950 μg/daily in order to control CS. Although such a high dose of the drug was never reported, no important side effects were registered. In our experience CS was well controlled by octreotide's 1500 μg/daily subcutaneous dose.

Ohnsmann and Sachsenheimer [23] reported the case of a young female suffering from multiple intracerebral metastases of bronchial carcinoid, treated with octreotide used in short term administration (3×100 μg/daily) for 8 weeks, in combination with daily dose of methyl-prednisolone 40 mg. With this medical therapy the patient became free from complaints and no increased growth of cerebral lesion was registered during a period of 9 months.

When octreotide fails, authors [24] recommend the use of alpha-interferon in the treatment of CS. Combination of octreotide and alpha-interferon might be of beneficial value in the long-term management of CS.

In conclusion, this is the largest series of atypical BC with liver metastases treated successfully with octreotide, reported in literature. Our results suggest the opportunity of a successful use of this drug in the management of CS when a more aggressive treatment is not feasible. Octreotide seems to improve significantly the survival rate of patients with liver metastases by carcinoid tumors. We observed two patients in whom a radically resected atypical carcinoid with liver metastases, died in 13 and 10 months, respectively, after chemotherapy. Octreotide was not used, as it is not yet disposable.

We also suggest the use of radiolabeled octreotide scintigtraphy in the preoperative study and in the follow-up of neuroendocrine tumors of the lung, because of its effectiveness in an early detection of the tumor, mediastinal or hilar lymph-node metastases and distant localization. A positive Octreoscan signifies the feasibility of a medical therapy with octreotide; which appears effective in the tumor's symptoms control and, in some cases, in its growth too. Finally, PCR technique's detection of somatostatin receptors sst_2–sst_5 in pathologic tissues is to be considered in all cases of lung neoplasm of neuroendocrine origin.

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Appendix A. Conference discussion

Dr T. Grodzki (*Szczecin, Poland*): I think not too many people have any experience with this type of treatment. But one thing was a little bit surprising for me, because when you showed the results, you showed seven patients, who are all alive, while two of them were refused to do anything. You told that they were in a poor performance status, that they were refused chemotherapy. Did you have any control group with no treatment at all?

Dr Filosso: We had five other patients which refused chemotherapy: they died within a median period of six months.

Dr D. van Raemdonck (*Leuven, Belgium*): Based on your good experience with this octreotide, do you think there is a role for prophylactic treatment in patients with positive receptors on the specimen?

Dr Filosso: Yes. In 1997 we published a paper in which we demonstrate the positivity of OctreoScan (in vivo expression of subtype2 somatostatin receptors) in neuroendocrine and non-neuroendocrine lung cancer.

So I think there is a possibility of using octreotide in adjuvant therapy in N2 neuroendocrine carcinoma of the lung. This is my opinion. No other papers are published till now concerning these data.

Dr P. Thomas (*Marseille, France*): I am a little bit surprised by your low incidence of metastases in your initial cohort of patients, only 7 among more than 100, and, second, by your high incidence of CS. It is possible but very unusual when the primary tumor is in the lung.

Dr Filosso: Well, as I reported, seven patients of our series had well differentiated neuroendocrine carcinoma of the lung (so called atypical carcinoid), and all presented liver metastases. We observed CS in all patient in which liver metastases were present.

Dr G. Friedel (*Gerlingen, Germany*): Have you measured somatostatin receptors in the primary tumor too? Are the receptors present in the primary too?

Dr Filosso: We had experience with our Pathologists who demonstrate the presence of somatostatin receptor subtype 2 both in primary tumor and in liver metastases. We published a paper about the use of Octreoscan in preoperative staging of neuroendocrine carcinoma of the lung, in which we demonstrate that neuroendocrine carcinoma in vivo expresses subtype 2 somatostatin receptor.