

Refractory neuroendocrine tumor—response to liposomal doxorubicin and capecitabine

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Background. A 61-year-old patient with no relevant medical or family history presented with a 2 month history of refractory dry cough that led to the diagnosis of typical carcinoid tumor of the lung metastatic to the mediastinal lymph nodes and liver. She initially received a long-acting somatostatin analog (octreotide) and chemotherapy with cisplatin and etoposide, which was ineffective.

Investigations. Physical examination, laboratory test, chromogranin A test, CT scan, ¹¹¹In-diethylenetriaminepenta-acetic acid (DTPA)-octreotide scan, ¹⁸F-FDG-PET scan, fine-needle and tissue core liver biopsies.

Diagnosis. Pulmonary spindle-cell carcinoid tumor with metastases to mediastinal lymph nodes and liver.

Management. Systemic treatment with oral capecitabine (1,500 mg/m² daily from day 1 to day 21) and intravenous liposomal doxorubicin (10 mg/m² on days 1, 8 and 15), both repeated every 4 weeks, administered concomitantly with long-acting octreotide 30 mg every 3 weeks. The patient achieved a significant and long-lasting response with the combination of capecitabine and liposomal doxorubicin. She reported no severe adverse effects.

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Learning objectives

Upon completion of this activity, participants should be able to:

- 1 Identify the natural history of carcinoid tumors.
- 2 List symptoms of carcinoid syndrome.
- 3 Diagnose carcinoid tumors effectively.
- 4 Specify the primary treatment of metastatic carcinoid tumors.

The case

A 61-year-old woman was referred to an oncology department because of a 2 month history of dry cough

Competing interests

The authors, the Journal Editor L. Hutchinson and the CME questions author C. P. Vega declare no competing interests.

that was refractory to standard treatment and evidence of a hilar lesion in the right lung on chest radiography. She had been diagnosed as having metastatic pulmonary neuroendocrine tumor. The patient's medical and family history was unremarkable; she had, however, smoked more than 20 cigarettes per day for over 20 years. Lung auscultation revealed a reduction in the normal respiratory sounds on the mid and low fields of the right hemithorax, while an abdominal examination demonstrated palpable hepatomegaly (approximately 8 cm), which was associated with moderate liver dysfunction (total bilirubin 21.5 μmol/l, aspartate aminotransferase [AST] 58 U/l, alanine aminotransferase [ALT] 130 U/l and γ-glutamyltranspeptidase [GGT] 1,725 U/l) at baseline blood test.

At the time of her presentation to the oncology department, the patient had a Karnofsky performance status of 90 (normal value 100). A chest and CT scan of her abdomen was subsequently performed, which showed a lesion in the middle of the right lung with a maximum diameter of 22 mm, a hilar lymph node with a maximum diameter of 30 mm adherent to the pulmonary artery and massive liver involvement with secondary lesions (Figure 1a–c). A liver biopsy showed histological features compatible with metastasis from a spindle-cell carcinoid tumor, without evidence of necrosis or mitoses. Immunohistochemistry performed on the liver tumor specimen showed intense reactivity for chromogranin A and negative staining for CK-POOL (a range of cytokeratins expressed in epithelial cells), TTF-1 (a thyroid

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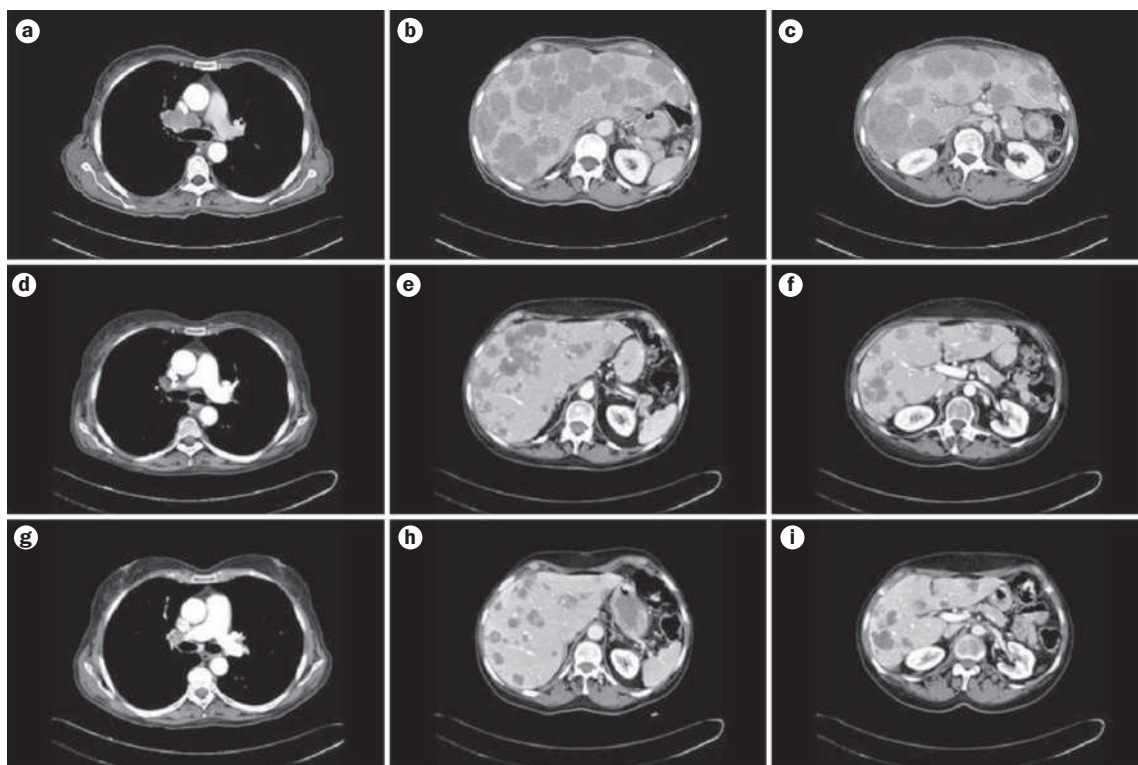


Figure 1 | CT scan images taken at baseline, after 4 cycles of chemotherapy and after cessation of this treatment. Images demonstrate the considerable reduction in dimensions and numbers of mediastinal and hepatic lesions from baseline (a–c) observed after four cycles (d–f) of combination chemotherapy with liposomal doxorubicin and capecitabine. Images g–i were taken 4 months after the end of chemotherapy, while the patient was receiving single-agent octreotide.

transcription factor marker expressed in lung and thyroid derived cells), CD99 (also known as MIC2 and expressed on all leukocytes but highest on thymocytes) and S100 (a low molecular weight protein mainly present in cells derived from the neural crest, such as Schwann cells, melanocytes and glial cells). The Ki67 proliferation index of the tumor was 42%. These features were consistent with a diagnosis of typical carcinoid tumor.^{1,2} This diagnosis was confirmed 1 month after the patient's referral to the oncology department.

We completed the patient's initial diagnostic work-up by performing DTPA-octreotide and CT scans. Abnormal radionuclide capitation was evident in the right parahilar area of the chest and in multiple areas of the liver. An FDG-PET scan was also performed and the results were comparable with those of the CT and octreotide scan. In view of the patient's disease burden, general condition and the results of blood analyses, we promptly initiated systemic therapy with a somatostatin analog. An intramuscular injection of 20 mg long-acting octreotide was administered every 4 weeks. After 2 months of treatment, a total-body CT scan was performed to assess the tumor response to this treatment, which was evaluated according to Response Evaluation Criteria in Solid Tumors (RECIST).³ CT images showed that the number of liver metastases had increased (from 10 to 18) and the dimension of the right lung mass had also increased (from

22 mm to 35 mm). The long-acting octreotide dose was then increased to 30 mg every 3 weeks. After a further 2 months of treatment, the results of additional CT and ¹¹¹In-octreotide scans were consistent with disease progression in the lung and liver.

We excluded the feasibility of peptide receptor radionuclide therapy because the ¹¹¹In-octreotide scan results were judged compatible with a nonspecific inflammatory and/or fibrotic process in the lung; the possible benefits of this approach in terms of antitumor activity would have been overwhelmed by its toxic effects.^{4,5} As initial therapy did not control the patient's disease, we decided to start combination chemotherapy with cisplatin (80 mg/m² on day 1) and etoposide (100 mg/m² on days 1, 2 and 3), which were both repeated every 3 weeks, with prophylactic granulocyte-colony stimulating factor support given on day 4. Intramuscular injection of long-acting octreotide 30 mg was concomitantly administered every 3 weeks. After three cycles of treatment, a CT scan showed disease stabilization in the chest and abdomen. The patient reported acoustic buzzing and partial hearing loss after the first two chemotherapy cycles, consistent with ototoxic effects of cisplatin. In view of these adverse effects and the marginal efficacy of this treatment, we decided to stop chemotherapy.

Evidence of progressive disease prompted our decision to treat the patient with two agents that are active against

Table 1 | Liver function analytes and plasma chromogranin A values during treatment

| Time point | Total bilirubin | | γ-Glutamyltranspeptidase | | Chromogranin A | |
|-------------------------|-----------------|-------|--------------------------|-------|----------------|-------|
| | μmol/l | (%) | U/l | (%) | μg/l | (%) |
| Baseline | 43 | (100) | 1,533 | (100) | 1,024 | (100) |
| Best response | 9 | (20) | 75 | (5) | 118 | (12) |
| Re-treatment initiation | 24 | (56) | 159 | (10) | 213 | (21) |
| Re-treatment response | 14 | (33) | 147 | (10) | 463 | (45) |

Values in parentheses are calculated as percentages relative to baseline.

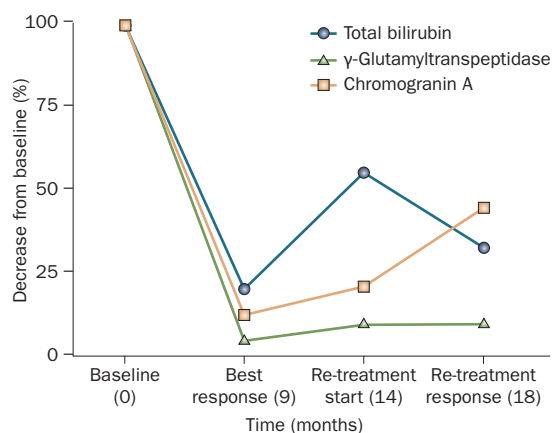


Figure 2 | Liver function analytes and chromogranin A values during treatment. The figure shows the course of total bilirubin, γ-glutamyl transpeptidase and chromogranin A plasma levels during treatment with capecitabine and liposomal doxorubicin plus long-acting octreotide. Values are calculated as percentages relative to baseline. Important time points (before treatment start, at the time of best response, at disease progression and at the time of best response after re-treatment with the same regimen) are represented.

neuroendocrine tumors: capecitabine (1,500 mg/m² days 1 to 21) and liposomal doxorubicin (10 mg/m² on days 1, 8 and 15), which were both repeated every 4 weeks. Long-acting intramuscular octreotide (30 mg) was concomitantly administered every 3 weeks. This treatment was well-tolerated, and the patient reported only grade 1 diarrhea and asthenia. After 2 months of treatment the patient's Karnofsky performance score had improved from 60 to 90, and her palpable hepatomegaly had decreased from 10 cm to 5 cm. Laboratory analyses demonstrated normalization of liver function: total bilirubin decreased from 43 μmol/l to 9 μmol/l, GGT from 1,533 U/l to 314 U/l and lactate dehydrogenase from 800 U/l to 493 U/l, while a total-body CT scan showed disease stabilization, with mild reductions in lung, mediastinal and liver lesions. The absence of severe adverse effects and the inadequate response to first-line chemotherapy prompted our decision to administer a further two cycles of combined capecitabine and

liposomal doxorubicin. A significant reduction in plasma chromogranin A levels (from 1,024 μg/l to 252 μg/l) and in the number of liver and thoracic lesions was consistent with a partial response according to RECIST criteria (Figure 1d–f). After four cycles of treatment, the patient continued single-agent octreotide 30 mg every 3 weeks. A CT scan performed after 5 months of octreotide monotherapy showed a further reduction of hepatic metastases and a minimal increase in chest lesion dimensions. These improvements continued to be compatible with a partial response (Figure 1g–i). The patient's plasma chromogranin A levels had decreased further, to 118 μg/l, and a physical examination were unremarkable (Table 1 and Figure 2). On the basis of these findings, we decided to continue intramuscular octreotide treatment (30 mg) every 3 weeks for a further 5 months.

At a follow-up visit, which was performed 13 months after treatment initiation, the patient reported a worsening cough and the onset of back pain. Her Karnofsky performance score was 70. Tumor evaluation by CT scan showed a significant increase in the dimensions of all metastatic lesions and disease progression was confirmed by an increase in her plasma levels of chromogranin A to 213 μg/l. In view of the patient's long progression-free survival (12.9 months), we decided to resume intramuscular octreotide (30 mg every 3 weeks) with capecitabine and liposomal doxorubicin chemotherapy at the same dose and schedule as used previously. After four cycles of such treatment, the patient's Karnofsky performance score improved slightly to 80, and she did not report any adverse effect attributable to chemotherapy. Despite an increase in plasma chromogranin A levels to 463 μg/l (Table 1 and Figure 2), imaging procedures demonstrated a mild reduction in liver lesion dimensions and stabilization of the pulmonary and mediastinal masses, which correlated with stable disease according to RECIST criteria. At a further follow up visit, performed 8 months after the initiation of re-treatment, we observed disease progression accompanied by deterioration in the patient's general condition. We decided to stop all antitumor treatment and to continue only with best supportive care. The patient died 31 months after the initial diagnosis.

Discussion of diagnosis

Neuroendocrine tumors are rare, malignant neoplasms derived from the neuroendocrine system. Carcinoid tumors are a subtype of neuroendocrine tumors that arise from argentaffin cells located in the foregut, midgut or hindgut; the midgut is the most common site of origin of these neoplasms, and they most often arise from the appendix.^{1,2,6} To this day, no clearly demonstrated risk factors for developing such tumors have been identified. Neuroendocrine tumors of the lung are generally classified into four categories: typical carcinoid, atypical carcinoid, large-cell neuroendocrine carcinoma and small-cell lung carcinoma (SCLC).² This classification also has prognostic implications: typical carcinoid tumors

are less aggressive than small-cell carcinomas.⁷ Carcinoid tumors can disseminate; regional lymph nodes and liver are the most common sites of metastases, followed by bone, lung, brain and other organs. The presence and the extent of liver involvement is one of the main determinants of survival,² as is demonstrated by the history of the patient we describe.

Patients with pulmonary carcinoid tumors can be asymptomatic even if they have metastatic disease. If symptomatic, symptoms can be related to the primary lesion (for example, cough, hemoptysis or pneumonia) or metastases. The onset of so-called carcinoid syndrome, which develops in approximately 13% of patients who have bronchial carcinoid tumors, is caused by secretion of 5-hydroxytryptamine, histamine or tachykinins into the systemic circulation by tumor cells.² Typically, carcinoid syndrome is characterized by attacks of cutaneous flushing, diarrhea and abdominal cramps, or by valvular cardiac manifestations due to fibrous deposits in the endocardium of the right side of the heart (which most often result in pulmonary stenosis and tricuspid regurgitation).⁸

Differential diagnosis

The patient we describe had a history of smoking, a dry cough that was refractory to standard treatment, and no evidence of symptoms related to carcinoid syndrome. In such circumstances, the diagnosis of lung cancer—either non-small-cell lung carcinoma (NSCLC) or SCLC—should be excluded. In fact, although a smoking habit remains the key etiological factor in both NSCLC and SCLC, it has no such role in carcinoid tumors. Moreover, NSCLC and SCLC occur much more frequently than bronchial carcinoid tumors.^{2–6}

A reliable differential diagnosis cannot be obtained by imaging procedures: in fact, evidence of a sharp central lesion and mediastinal lymph-node enlargement on thoracic CT scan is indicative of squamous-cell carcinoma, SCLC and carcinoid tumor. Moreover, although ¹¹¹In-DTPA-octreotide scans have high sensitivity for the localization and staging of carcinoids (which express high-affinity somatostatin receptors; in 88–100% of cases, such expression is present in both the primary tumor and metastases),⁹ positive results can also be observed in SCLC.¹⁰

In the patient we describe, a definitive diagnosis was finally reached after performing fine-needle aspiration and tissue-core biopsy of a liver lesion. Cytologic analysis revealed spindle-shaped small cells with scant cytoplasm, which excluded the diagnosis of NSCLC. Histologic staining revealed elevated expression of chromogranin A (a marker of neuroendocrine differentiation, as are neuron-specific enolase and synaptophysin), which confirmed the diagnosis of carcinoid tumor. Increased expression of chromogranin A, however, can be present in SCLC and, to a lesser extent, NSCLC (Figure 3). The lack of immunoreactivity for keratin and epithelial membrane antigen, which is a characteristic feature of SCLC, confirmed the diagnosis of spindle-cell carcinoid tumor.¹²

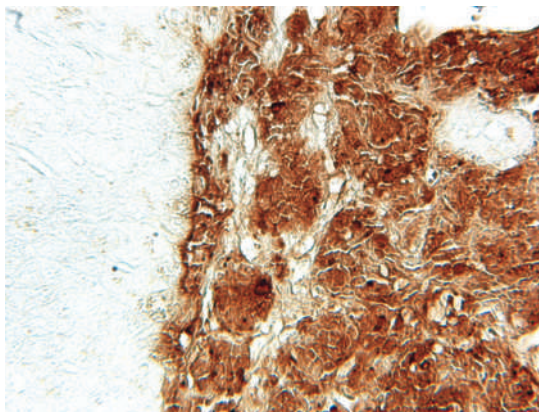


Figure 3 | Photomicrograph of a liver biopsy sample immunostained for chromogranin A. Tumor cells show intense staining for the neuroendocrine marker chromogranin A using the LK2H10 monoclonal antibody (Ventana, Tucson, AZ, USA). Magnification $\times 40$.

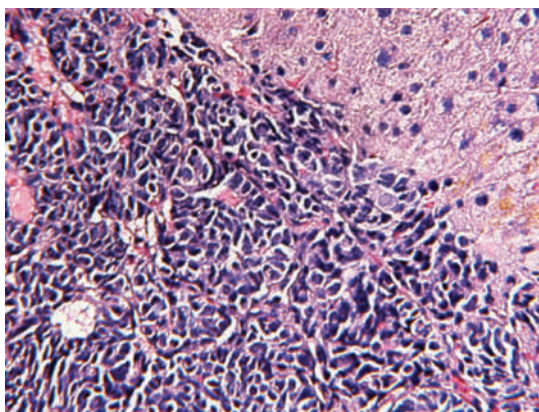


Figure 4 | Photomicrograph of a liver biopsy sample stained with hematoxylin and eosin. The specimen shows spindle cells with hyperchromatic nuclei and scant cytoplasm. The cells are organized in nest-like structures, with no evidence of mitoses or necrosis (magnification $\times 40$).

Two main criteria are commonly used to identify the pathological subtypes of carcinoid tumors: the mitotic count and the presence of necrotic areas.¹¹ Fewer than two mitoses per 2 mm^2 and a lack of necrosis, as demonstrated in samples from the patient described here, are distinctive features of typical carcinoid tumors (Figure 4), whereas atypical carcinoid tumors are characterized by the presence of necrosis and 2–10 mitoses per 2 mm^2 .

Treatment and management

Few chemotherapy regimens are active and effective in the treatment of metastatic carcinoid tumors.^{2,12,13} Patients with these tumors are generally treated with somatostatin analogs, especially those who have a positive octreotide scan or symptoms of carcinoid syndrome. These agents can control hormone-mediated symptoms and might exert an antiproliferative (tumorstatic) effect that limits

tumor growth and results in tumor stabilization rather than shrinkage.² Similarly, radiolabeled somatostatin analogs have been used to control the disease and, in some cases, objective responses have been reported.¹⁴

In patients who fail to demonstrate disease control with somatostatin analog therapy or who have a poor prognosis, chemotherapy is generally considered a reasonable treatment option.¹ Unfortunately, the results of systemic chemotherapy have generally been disappointing: single-agent and combination chemotherapy both achieve low tumor response rates (0–30%), with short duration of responses (less than 1 year). Moreover, no data suggest that second-line chemotherapy will be effective after the failure of the first-line treatment.^{1,2} We chose a combination of oral capecitabine and liposomal doxorubicin because these agents have a favorable toxicity profile. This combination is, therefore, a rational chemotherapy regimen, in view of the different mechanisms of action of these two agents and their non-overlapping adverse-effect profiles. Oral capecitabine and liposomal doxorubicin seems to be a potentially more active regimen than monotherapy with a fluoropyrimidine, anthracycline or temozolomide. Our experience suggests that this regimen is

feasible, apparently without severe adverse effects. In a pretreated patient with high tumor burden and initial liver dysfunction, this combination achieved a partial response (and remarkable control of symptoms) that persisted for almost 13 months of follow-up. Moreover, treatment rechallenge after a chemotherapy-free interval resulted in disease control and symptomatic improvement.

Conclusions

Even though suboptimal efficacy and a high incidence of severe toxic effects have been reported, cisplatin and etoposide are still the chemotherapeutic agents most widely used to treat metastatic neuroendocrine tumors. Our experience suggests that fluoropyrimidines and anthracyclines can be safely administered in combination in this setting, and that these agents may have activity against neuroendocrine tumors that progress despite somatostatin analog therapy. The results obtained, in terms of antitumor effect and symptom control, indicate that the regimen we designed may be a useful treatment option for patients with metastatic carcinoid tumors in whom other strategies have failed to control disease progression.

1. NCCN Clinical Practice Guidelines in Oncology. National Comprehensive Cancer Network: your best resource in the fight against cancer [online], http://www.nccn.org/professionals/physician_gls/f_guidelines.asp (2009).
2. De Vita, V. T Jr et al. in *DeVita, Hellman, and Rosenberg's Cancer: Principles & Practice of Oncology*, 8th edn Ch. 44 (Lippincott, Williams & Wilkins, Philadelphia, 2008).
3. Therasse, P et al. New guidelines to evaluate the response to treatment in solid tumors. European Organization for Research and Treatment of Cancer, National Cancer Institute of the United States, National Cancer Institute of Canada. *J. Natl Cancer Inst.* **92**, 205–216 (2000).
4. Granberg, D. et al. Octreoscan in patients with bronchial carcinoid tumours. *Clin. Endocrinol. (Oxf.)* **59**, 793–799 (2003).
5. Musi, M. et al. Bronchial carcinoid tumours: a study on clinicopathological features and role of octreotide scintigraphy. *Lung Cancer* **22**, 97–102 (1998).
6. Oberg, K. Carcinoid tumors: molecular genetics, tumor biology, and update of diagnosis and treatment. *Curr. Opin. Oncol.* **14**, 38–45 (2002).
7. Asamura, H. et al. Neuroendocrine neoplasms of the lung: a prognostic spectrum. *J. Clin. Oncol.* **24**, 70–76 (2006).
8. Anderson, A. S. et al. Cardiovascular complications of malignant carcinoid disease. *Am. Heart J.* **134**, 693–702 (1997).
9. Kwekkeboom, D. J. et al. Somatostatin analogue scintigraphy in carcinoid tumours. *Eur. J. Nucl. Med.* **20**, 283–292 (1993).
10. Tzannou, I. A. et al. The use of radiolabeled somatostatin analog scintigraphy in the staging of small cell lung cancer patients. *Am. J. Clin. Oncol.* **30**, 503–506 (2007).
11. Gustafsson, B. I. et al. Bronchopulmonary neuroendocrine tumors. *Cancer* **113**, 5–21 (2008).
12. Kosmidis, P. A. Treatment of carcinoid of the lung. *Curr. Opin. Oncol.* **16**, 146–149 (2004).
13. Bajetta, E. et al. Update on the treatment of neuroendocrine tumors. *Expert Rev. Anticancer Ther.* **3**, 631–642 (2003).
14. Buscombe, J. R. et al. Long-term efficacy of high-activity ¹¹¹In-pentetreotide therapy in patients with disseminated neuroendocrine tumors. *J. Nucl. Med.* **44**, 1–6 (2003).

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