Marked response to a cisplatin/docetaxel/temozolomide combination in a heavily pretreated patient with metastatic large cell neuroendocrine lung carcinoma

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At present, there is no clear consensus on the most appropriate treatment approach for large cell neuroendocrine carcinoma of the lung. Large cell neuroendocrine carcinoma lesions differ from other nonsmall cell lung carcinomas in that they have a particularly aggressive clinical behaviour and extremely poor prognosis. We report a 52-year-old woman large cell neuroendocrine carcinoma patient with progressive stage IV disease in the chest, liver, adrenal glands and, particularly, the brain, who achieved a marked response to a fourth-line combination of docetaxel, cisplatin and temozolomide. This regimen significantly improved her quality of life and survival. The good response obtained in this heavily pretreated patient adds to the evidence regarding the use of temozolomide in patients with lung cancer with brain metastases. ***Anti-Cancer Drugs*** **18:1227–1230 © 2007 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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Introduction

Large cell neuroendocrine carcinomas (LCNEC) of the lung are rare, comprising approximately 3% of resected pulmonary lesions [1]. LCNEC was originally proposed as an independent histological subtype by Travis *et al.* in 1991 [2], who suggested an addition to the existing neuroendocrine subclassifications of typical carcinoid, atypical carcinoid and small cell lung cancer (SCLC) [2]. Although the disease has traditionally been considered to be a nonsmall cell lung cancer (NSCLC), it has a particularly aggressive clinical behaviour. LCNEC is therefore distinctly different from other NSCLC subtypes, with an extremely poor prognosis even for early-stage disease and overall survival rates similar to those seen for SCLC [1,3,4]. We report a dramatic response in a heavily pretreated LCNEC patient receiving a fourth-line combination of docetaxel/cisplatin/temozolomide.

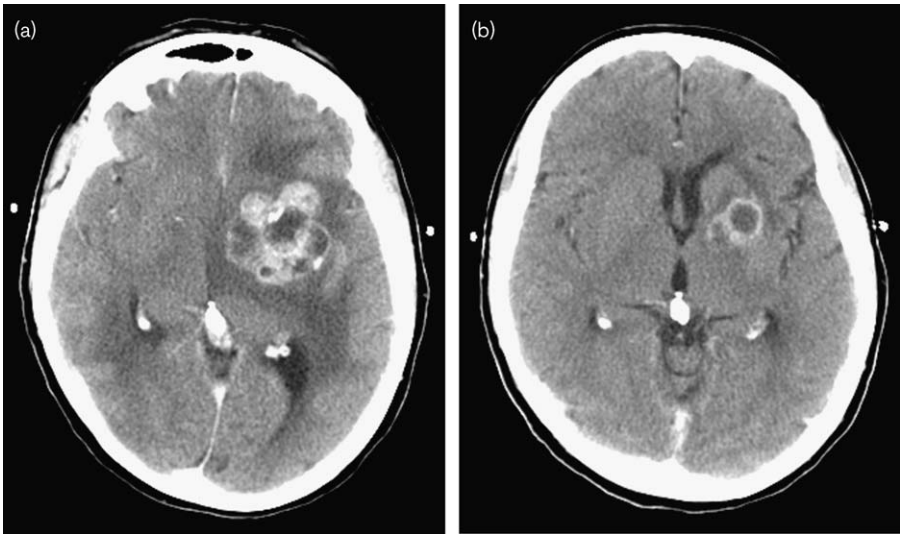
Case report

A 52-year-old woman exsmoker presented in September 2003 with increasing shortness of breath and a cough for 3 months. Chest radiography confirmed that the patient had superior vena cava obstruction that was treated with stent insertion, resulting in relief of symptoms. A rigid bronchoscopy was performed, and a 10-mm endobronchial lesion in the right bronchus was identified and biopsied. Histological analysis showed closely packed large malignant epithelial cells infiltrating connective tissue, and arranged in organoid and trabecular groups. These cells had a low nuclear: cytoplasmic ratio, contained large oval or polygonal nuclei with fine chromatin, and showed frequent mitoses and widespread necrosis. Immunohistochemistry was consistent with LCNEC of lung origin (positive chromogranin, synaptophysin, PGP 9.5, CD56, TTF-1 and cytokeratin 7 with negative cytokeratin 20). Computed tomography (CT) indicated bulky mediastinal disease, with a small peripheral lesion in the right upper lobe and involved cervical lymph nodes.

First-line treatment comprised cisplatin and etoposide every 21 days. Response to this treatment was minimal with radiologically stable disease. Therefore, after three cycles, the treatment regimen was switched to concurrent chemoirradiation, delivering 40 Gy in 2-Gy fractions to the mediastinum. The chemotherapy was carboplatin and paclitaxel weekly which continued after radiotherapy. The patient tolerated the treatment (which was completed in March 2004) well and showed good symptomatic benefit with a partial radiological response.

However, soon after completing this second-line treatment the patient developed neurological symptoms, and two brain metastases (one 5 cm in diameter) were identified on CT scan. Whole-brain radiotherapy (WBRT) was therefore given in April 2004, delivering 30 Gy in 10 fractions, with a good symptomatic and a radiological partial response. By June 2004, although the disease had progressed bilaterally in the perirenal fat, the patient

Fig. 1



Computed tomography images showing the brain disease before treatment [(a) September 2004] and the good response following administration of the docetaxel, cisplatin and temozolomide combination [(b) November 2004].

continued to feel well, and the mediastinum and brain remained controlled. She was subsequently started on gefitinib. By September 2004, however, the patient was deteriorating, and a further CT scan confirmed massive disease progression in the lungs, mediastinum, liver, perirenal regions, right adrenal and, particularly, in the brain. At this point, she was offered palliative care alone. After a request for more treatment from both the patient and her family, a docetaxel, cisplatin and temozolomide triplet combination was administered starting in September 2004 (cisplatin 40 mg/m^2 intravenously on day 1; docetaxel 25 mg/m^2 intravenously on days 1, 8, 15; temozolomide 150 mg/m^2 orally on days 1–5). Treatment was repeated every 4 weeks. The choice of regimen was based on a single case report in metastatic NSCLC [5].

The patient received four cycles of this regimen up to mid-December 2004. An excellent symptomatic and radiological response was seen (Fig. 1a and b), with a marked improvement in her quality of life that enabled her to return to full activity. CT in November 2004 confirmed a good partial response in all regions including the brain, mediastinum, liver and kidneys. Unfortunately, the disease started to progress again by the end of December 2004 (initially as a breast lump) and the patient died in April 2005, surviving a total of 20 months from presentation.

Discussion

LCNEC is a rare tumour. The tumour is traditionally considered to fall within the category of poorly differentiated NSCLC. These tumours, however, have certain characteristic histological hallmarks of neuroendocrine lesions – both morphological and immunohistochemical – and, indeed, these characteristics are required for the diagnosis. In terms of clinical outcome, a number of groups have reported that LCNEC patients have a significantly worse survival after resection than patients with the histologically similar large cell carcinomas and other NSCLC, with outcomes similar to the highly metastatic SCLC [1,6,7]. In addition, the propensity of the disease to metastasize early in its clinical course, often to the brain, shows a marked similarity to SCLC. The rarity of LCNEC makes large trials difficult and, therefore, conclusions tentative. This factor undoubtedly contributes to the current lack of a consensus on chemotherapy and indeed overall management for this disease.

In most small case series and case reports, initial treatment for unresectable disease has been platinum-based chemotherapy combinations active in SCLC, such as cisplatin and etoposide. Indeed, in a series of 83 patients with pure pulmonary LCNEC from Italy, cisplatin/etoposide chemotherapy was the single most important variable in predicting increased survival [8]. Data to guide second- or third-line treatment are very scant in LCNEC. We chose to use chemoradiotherapy with carboplatin and paclitaxel (a combination active in SCLC), and subsequently gefitinib. In a small Japanese case series of five patients treated with gefitinib as salvage treatment, one achieved a partial response [9]. Our patient responded to WBRT, again demonstrating in our experience, the radiosensitivity of LCNEC tumours.

To our knowledge, this is the first report on the use of a temozolomide-containing regimen in LCNEC and the second only of a lung cancer patient treated with this regimen. Docetaxel/platinum combinations are used extensively in the treatment of metastatic lung cancer. Our rationale for the inclusion of temozolomide in the regimen rested on the known ability of this agent to cross the blood–brain barrier. Temozolomide is an oral, bioavailable, second-generation alkylating agent that is generally well tolerated, and has recently demonstrated efficacy in the treatment of NSCLC and SCLC patients with brain metastases in phase II trials and small case series [10,11].

Christodoulou *et al.* [10] reported a phase II trial comprising 32 patients (of whom 12 had NSCLC) with solid tumours and recurrent or progressive brain metastases. The combination of cisplatin and temozolomide achieved at least a partial response in the brain in 10 (31.2%) patients with stable disease in a further 16%. Twenty-eight percent showed response in extracranial sites. All the patients with response in the extracranial sites had also responded in the brain. It is worth noting that one patient with NSCLC achieved a complete response in both the brain and the thorax. The majority of the responders (six out of 10 patients), however, had breast cancer and therefore presumably more chemosensitive disease. Median overall survival for all patients (85% of which had received prior chemotherapy, 53% prior WBRT) was 5.5 months and time to progression 2.9 months.

In a dose-escalation phase I trial of vinorelbine and temozolomide in patients with pretreated progressive or recurrent brain metastases, 44% of the patients had stable disease or response to treatment, with a median survival of more than 6 months. Thirteen of the 21 patients in that study had lung cancer (10 NSCLC and three SCLC) [12]. These response rates refer to brain metastases only, as systemic responses were not systematically evaluated.

Single-agent temozolomide may be less effective. In a series of 30 NSCLC patients (with progressive/recurrent brain metastases after WBRT), stable disease or response to single-agent temozolomide was seen in 20%. The chemotherapy was well tolerated [11]. In another series of 41 patients (24 with lung cancer) with recurrent brain metastases, however, single-agent temozolomide achieved stable disease or response in the brain in 41% with a median survival of 6.6 months. Of the 24 patients with a lung primary, the rates for response and stable disease in the brain were 9.1 and 36.4%, respectively, with one patient responding in both the brain and mediastinum [13].

Temozolomide administered concurrently with WBRT resulted in improved rates of objective response and symptomatic improvement, but not overall survival, in a Greek phase II trial compared with WBRT alone [14]. In this study, 40 of the 48 patients had a lung primary with previously untreated brain metastases and the objective response rate in the brain was 23% in the combination arm versus 14% in the WBRT alone arm. Response rates for extracranial disease were not reported.

In a Spanish phase II trial in patients with previously untreated brain metastases (42 of the 82 patients had a lung primary), concurrent administration of WBRT and temozolomide resulted in significantly improved brain-related progression-free survival, with acceptable toxicity compared with WBRT alone. The cause of death was neurologic in 69% of WBRT patients compared with 41% in the combination treatment group, but there was no difference in overall survival [15]. Moreover, the trial stopped early due to lack of recruitment, reflecting the oncologists' reluctance to withhold chemotherapy other than temozolomide for systemic disease for the duration of the trial. In this respect, combination regimens such as ours have the advantage of treating both the intracranial and the systemic disease.

The results in patients with pretreated or recurrent metastatic disease question whether temozolomide would be effective as a first-line regimen. A European Organisation for Research and Treatment of Cancer trial attempted to answer that question. Twenty-five patients with NSCLC (12 with brain metastases and 13 without) were given single-agent temozolomide. The study had to be stopped early as there were no objective responses in either group with evidence of early disease progression [16]. The authors did not report on whether the progression was primarily intracranial or extracranial, or both.

A French phase II trial assessed the efficacy of cisplatin and temozolomide combination as up-front treatment in patients with NSCLC and brain metastases. Fifty patients were recruited to receive up to six cycles of cisplatin and temozolomide, followed by radiotherapy in case of either progressive disease at any time or stable disease after four cycles. Objective responses were seen in only 16% of patients and median survival was 5 months. After two cycles, the response rates at the brain and the primary tumour were 12% at each site [17].

Our case report adds to the literature on the use of temozolomide-containing regimens in pretreated advanced lung cancer, being the first one to demonstrate response in a patient with LCNEC. This well-tolerated treatment, based on a novel chemotherapy combination to treat optimally both systemic and intracranial disease, markedly improved our patient's quality of life and extended her survival.

The primary tumour type most likely to metastasize to the brain is lung cancer. In patients who have failed

WBRT, palliative care is usually the only available management option. For fit patients temozolomide singly or preferably in combination may offer a real alternative. As a separate issue we need to develop new ways to reduce the risk of brain metastases in patients who have controlled extracranial disease. In SCLC and LCNEC, we routinely now give prophylactic cranial irradiation to appropriate patients. Prophylactic cranial irradiation is currently under investigation for NSCLC as well. Another possible approach may be to incorporate temozolomide in first-line chemotherapy regimens.

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