Abstract. Background: The activity of sunitinib, a multitargeted tyrosine kinase inhibitor with antiangiogenic and antitumor activities, has been explored in several solid malignancies such as breast, lung, prostate and pancreatic cancer. Currently it is approved for the treatment of metastatic renal cell carcinoma and gastrointestinal stromal tumors. Non-small cell lung cancer usually presents at an advanced or metastatic stage at diagnosis. Treatment options are limited for this disease, therefore symptom palliation and patient’s quality of life are primary objectives of therapy. Case Report: We describe the case of a patient (male, 67 years old) with heavily pre-treated metastatic non-small cell lung carcinoma who received sunitinib according to the following 3-week schedule: 50 mg daily for 2 weeks followed by a 1-week rest. The patient completed six months of therapy achieving a major disease response without high-grade toxicities. Conclusion: In this case, sunitinib shows promising single-agent activity in pretreated non-small cell lung cancer, with a good toxicity profile and flexible administration schedule.

Non-small cell lung cancer (NSCLC) represents a leading cause of cancer-related death in Western countries since the majority of patients present with a locally advanced or metastatic disease at diagnosis (1). For these patients, treatment options are therefore limited and long-term survival is typically less than one year. Patients with good performance status are candidates for systemic therapy, primarily consisting of a platinum-based doublet that represents the standard of care in this setting (2). Recently, preclinical and clinical studies have identified crucial molecular pathways in NSCLC including receptors of VEGF and platelet-derived growth factor (PDGFR), both of which play an important role in tumour growth and neoangiogenesis (8). Thus PDGF as well as VEGF are rational targets for anticancer therapy in NSCLC.

Sunitinib malate is an orally bioavailable multitargeted tyrosine kinase inhibitor with proven antiangiogenic and antitumor activities, having time-dependent and dose-dependent anti-proliferative effects (9). Exposure to sunitinib leads to stepwise alterations in the endothelial cell layer resulting in blood congestion and necrosis of centrally located tumor cells. Moreover, a direct antitumor effect has also been described. This drug specifically inhibits VEGFR-1, -2 and -3, PDGFR-α and -β, stem cell growth factor (KIT), FMS-like tyrosine kinase 3 (FLT3), colony-stimulating factor 1 receptor (CSF-1R) and glial cell line-derived neurotrophic factor receptor (RET) (10). Phase III trials with sunitinib in metastatic renal cell carcinoma and imatinib intolerant or resistant gastrointestinal stromal tumors have shown unexpected survival rates with acceptable toxicity (11, 12). Sunitinib is currently approved for the treatment of those diseases. Recently, interesting preclinical and clinical studies have suggested a possible clinical development of sunitinib in the treatment of solid tumors, including breast cancer and NSCLC (13-16).
Here we report the case of a 69-year-old male affected by NSCLC (with squamous histology) who received sunitinib as fourth-line treatment.

Case Report

In June 2007, a 67-year-old male presented to our institution with a locally advanced lung carcinoma. In 1991, he had undergone a radical left pneumonectomy followed by radiotherapy for a lung squamous cell carcinoma involving the left main bronchus. Years later, he had been diagnosed with moderate chronic obstructive pulmonary disease and type II diabetes treated with sulfonylureas, with good glycometabolic control. At the beginning of 2007, the patient presented cough and increasing dyspnea. A chest X-ray showed the presence of a solid nodule (3 cm in maximum diameter) involving the right lung hilum, suggestive of malignancy. Bronchoscopy revealed the presence of bleeding neoplastic tissue that was almost completely occluding the right main bronchus. The pathomorphological assessment of the lesion specimen revealed a poorly differentiated lung squamous cell carcinoma. Immunohistochemical assays revealed cytokeratin-7 and P-63 positivity and CD-56, CD-20, TTF-1, and synaptophysin negativity. A whole-body computerised tomography (CT) scan confirmed the presence of neoplastic tissue involving the right lung hilum and parahilar right lymph nodes without other metastatic localizations (Figure 1).

Considering the patient’s clinical condition and past pneumonectomy, a platinum-vinorelbine chemotherpay regimen was begun for six courses. This was followed by a radiation treatment targeting neoplastic tissue with a total dose of 30 Gy. A new CT scan performed in July 2008 showed a significant reduction of tumor size in the right lung (10 mm) with an almost complete regression of hilar lymph node metastases (Figure 2). Three months later, a new CT scan demonstrated the occurrence of new metastatic sites involving the left inferior lobe (11 mm in maximum diameter) and the IV hepatic lobe (20 mm in maximum diameter) (Figures 3 and 4). Therefore, we planned a second-line chemotherapy regimen with gemcitabine plus docetaxel. The patient continued chemotherapy for a total of eight courses without major toxicities, achieving stabilization of lung lesions (according to RECIST criteria Ver 1.1, 2009) and complete regression of the hepatic lesion. However, in May 2009, due to new disease progression, characterized by volume increase of lung localizations, a daily 150 mg administration of erlotinib was started. After four weeks of treatment, the patient developed a G3 cutaneous toxicity according to WHO toxicity criteria (Ver 3.1) that required the reduction of the erlotinib dose to 100 mg daily. The erlotinib therapy was continued for a total of six months, with good disease control.

In October 2009, a new CT scan showed an increase of primary and metastatic lung involvement (Figure 5). Therefore, considering the patient’s desire to continue...
treatment, his good performance status and the absence of other co-morbidities such as hypertension, cardiovascular disease and thyroid dysfunction, we proposed a daily administration of 50 mg sunitinib for three weeks according to the following schedule: 2 weeks on, followed by 1 week off. This schedule has been employed at our center for other patients affected by kidney malignancies, showing a good safety and tolerability profile. Drug administration was approved by the local Ethics Committee. During treatment, the patient experienced grade 2 fatigue with a slight increase of thyroid-stimulating hormone that did not require levotyroxine administration. During treatment, no variations in left ventricular function or increase in blood pressure were reported, especially during the on periods as compared to baseline. No hematological toxicity was observed and overall treatment was generally well tolerated.

After two months of sunitinib administration, a CT scan showed disease stability, with a minor volume reduction in the lung metastatic node (Figure 6). Therefore, we decided to continue sunitinib administration on the same schedule. After 6 months of treatment, a complete disease restaging was planned, with a 18F-deoxyglucose positron-emission tomographic scan (Figure 7) that revealed the absence of hypermetabolic activities in the known neoplastic areas and only a reduced glycometabolic activity with insignificant standardized uptake value range. Presently, the patient is in good clinical condition and still taking sunitinib according to the same three weeks schedule.
Preclinical and clinical studies have identified critical pathways in NSCLC including VEGF and PDGF, both of which play an important role in tumor growth and progression. As in most solid tumors, in NSCLC it is also believed there is a multilevel cross-stimulation among targets along several pathways of signal transduction that leads to malignancy. Therefore, a logical therapeutic approach suggests the use of a multitargeted single agent to provide a more complete therapeutic benefit. Such agents include a number of small-molecule tyrosine kinase inhibitors that target several receptors of tyrosine kinases associated with NSCLC and activated endothelial cells, resulting in direct targeting of both tumor and blood vessels, higher likelihood of single-agent activity and lower toxicity rates.

Preclinical data showed benefits of combining VEGFR and PDGFR inhibition in the H266 human lung carcinoma model (17). Single-agent sunitinib resulted in antitumor activity similar to that observed with the combination of a PDGFR/KIT inhibitor together with a single-agent VEGFR inhibitor and was superior to each agent administered alone, supporting the importance of dual PDGFR/VEGFR inhibition for antitumor activity. These pathways play an important role in NSCLC, as confirmed by recent trials with the anti-VEGF monoclonal antibody bevacizumab, showing that the addition of this drug to chemotherapy can improve survival compared to chemotherapy alone (3). Recently, a phase II trial with sunitinib alone in heavily pretreated NSCLC patients has shown interesting antitumor activity of this drug (16).

In the reported case, daily 50 mg sunitinib was administered to a patient with metastatic NSCLC according to a fractionated schedule (50 mg daily for 2 weeks followed by 1 week of rest) that was preferred over the standard 6-week schedule for its better toxicity profile while maintaining the same dose intensity over a 6-week period. We consider this an important feature of sunitinib administration as it offers flexible therapeutic options that can be adapted to patients with different needs and reported toxicities, even during the same cycle. For our patient, the 2-week daily administration period resulted in only low-grade toxicities with complete recovery during the off period. This is an important issue in NSCLC therapy, especially in heavily pretreated patients, as severe toxicities are common and patients present a poor performance status due to the extent of disease.

The treatment has proven to be safe and well tolerated and the patient did not experience adverse events > grade 2 WHO toxicity. However, complete recovery from toxicities, in particular mucositis, was observed during the rest period, resulting in an excellent patient adherence to the treatment schedule. Our findings suggest that sunitinib has an acceptable tolerability profile, with manageable and reversible adverse events, and can be administered using a flexible dosing schedule to meet the individual patient needs. Finally, sunitinib has provocative single-agent activity in previously treated patients with recurrent and advanced NSCLC, with a level of activity similar to currently approved agents.

Given the available evidence for sunitinib activity in NSCLC patients, additional studies are currently needed to...
assess the feasibility of using sunitinib in association with chemotherapy or other molecularly targeted agents, or as maintenance therapy in patients who derived clinical benefit after a first-line platinum-based doublet.

Acknowledgements

The Authors acknowledge the assistance of Professor Grazia Cini in editing the manuscript.

Funding for this study was provided by the Associazione Toscana Ricerche e Cure Oncologiche, Florence, Italy.

References


