

Safety of Nab-paclitaxel plus Sunitinib: Analysis of Three Cases

ARKADIUSZ Z. DUDEK and SHEILA NGUYEN

Division of Hematology, Oncology and Transplantation, University of Minnesota, Minneapolis, MN, U.S.A.

Abstract. *Background: Second-line treatment options are limited in controlling advanced thoracic cancer in patients who have progressed following first-line chemotherapy. Case Report: The safety of combination therapy with nab-paclitaxel, an albumin-bound paclitaxel, and sunitinib, a tyrosine kinase receptor inhibitor, was evaluated retrospectively in three patients with advanced, previously treated metastatic esophageal cancer, non-small cell lung cancer (NSCLC), and small cell lung cancer (SCLC), respectively. Results: Grade 3 and 4 toxicities were mainly hematological and manageable. A notable improvement in cancer symptoms and reduction in tumor size were seen in all three patients. Conclusion: Based on the easily managed toxicities and apparent efficacy of the regimen of weekly nab-paclitaxel and daily sunitinib, we conclude that further evaluation is warranted to assess the efficacy of this combination therapy in previously chemotherapy-treated patients with advanced thoracic cancer.*

The overall 5-year survival rate for patients with lung or esophageal cancer is approximately 16%; however, patients with advanced thoracic cancer have significantly lower survival rates (1). The current therapy for patients with advanced non-small cell lung cancer (NSCLC) is chemotherapy and radiation for patients with locally advanced disease, or combination chemotherapy for patients with metastatic disease (2). Patients initially receive a platinum-based combination with a taxane, gemcitabine, or etoposide. Second-line therapies include docetaxel, pemetrexed, and erlotinib. The recommended initial treatment for patients with extensive-stage small cell lung cancer (SCLC) is combination chemotherapy, primarily with a platinum doublet, with whole-brain radiation for brain

metastasis and focal radiation therapy for symptomatic lesions (3). Patients with metastatic esophageal cancer are treated with either a taxane, 5-FU, or platinum-based chemotherapy (4).

Nab-paclitaxel is the first novel delivery system for taxanes approved by the FDA. Nab-paclitaxel, a nanoparticle albumin-bound form of paclitaxel, was designed to provide improved drug delivery to tumor cells and improved antitumor activity while also providing a more favorable toxicity profile compared with Cremophor EL-paclitaxel. A higher dose (50%) of paclitaxel can be administered because of the lower toxicity and absence of solvents in the nab-paclitaxel formulation. Furthermore, nab-paclitaxel may partition into tumor cells better than paclitaxel, leading to higher concentrations in the tumor cells. Although taxanes may enter tumor cells *via* passive diffusion, nab-paclitaxel may also enter the cell *via* active transport and *via* interactions with specialized transport proteins (*e.g.* caveolae and SPARC) (5, 6).

Nab-paclitaxel demonstrated efficacy in patients with lung cancer and was well tolerated. Patients with previously untreated advanced NSCLC who received weekly nab-paclitaxel and carboplatin experienced an objective response rate of at least 36% and a median survival of approximately 11 months. Additionally, this regimen was well tolerated, with a low incidence and severity of peripheral neuropathy (7). Patients with previously untreated advanced NSCLC who received nab-paclitaxel as a single agent every 3 weeks had an overall response rate of 16%, a median time to progression of 6 months and a median survival of 11 months (8). Treatment was well tolerated, with grade 3 adverse events including neutropenia (9%), fatigue (7%) and sensory neuropathy (5%), and no grade 4 toxicities. In a study of weekly nab-paclitaxel in patients with advanced chemo-naive NSCLC, in which a response rate of 30% and median survival of 11 months were observed, the incidence of sensory neuropathy was reduced simply by prolonging the infusion time (9, 10).

The addition of antiangiogenic agents such as bevacizumab or tyrosine kinase inhibitors such as sunitinib or sorafenib to traditional chemotherapy is associated with increased efficacy compared to chemotherapy alone. Progression-free survival and overall survival were increased

Correspondence to: Arkadiusz Dudek, MD, Ph.D., Associate Professor of Medicine, Division of Hematology, Oncology and Transplantation, University of Minnesota, 420 Delaware Street SE, MMC 480, Minneapolis, MN 55455, U.S.A. Tel: +1 6126240123, Fax: +1 6126256919, e-mail: dudek002@umn.edu

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in patients with previously treated locally advanced or metastatic NSCLC receiving bevacizumab in combination with docetaxel or pemetrexed alone (11). Bevacizumab also increased overall survival in combination with paclitaxel and carboplatin in patients with previously untreated NSCLC compared with patients who received paclitaxel and carboplatin alone (12). Both sorafenib and sunitinib have been tested as single-agent therapy for patients with relapsed or refractory NSCLC with modest activity (13).

Because of the efficacy of both nab-paclitaxel and sunitinib as single-agent therapy in patients with metastatic thoracic cancer, it is reasonable to assume that these agents in combination may have significant activity. The purpose of this paper is to describe the safety of the combination of nab-paclitaxel and sunitinib administered to three patients with either previously treated metastatic esophageal, NSCLC, or SCLC (Table I).

Case 1

A 63-year-old male presented to the University of Minnesota with a history of esophageal cancer, diagnosed in May 2006, with development of metastases to multiple mediastinal lymph nodes in October 2006 along with a parietal brain metastasis that was resected (Figure 1A). He was initially treated with cisplatin 30 mg/m² and irinotecan 65 mg/m² every 6 weeks on days 1, 8, 15 and 22. The patient completed 2 cycles of this therapy but had disease progression with a small new brain metastasis requiring stereotactic radiosurgery. The patient had symptoms of low back pain, poor appetite, a 30- to 40-pound weight loss, constipation, nausea, vomiting, confusion, and depression. The patient's vital signs and physical examination were unremarkable and laboratory parameters were normal except for a hemoglobin of 10.3 g/dl and a creatinine of 1.75 μmol/l. A chest computed tomography (CT) showed a left pleural effusion with progression of mediastinal, retrocrural and pulmonary window lymphadenopathy (Figure 2A). A CT of the abdomen showed a large retroperitoneal mass associated with the distal esophagus and increased retroperitoneal and mediastinal adenopathy. The patient developed intractable back pain that was treated with a celiac plexus neurolytic block and later by placement of an intrathecal morphine pump.

In February 2007, the patient began therapy with weekly nab-paclitaxel 125 mg/m² via 30-minute infusion on days 1, 8, and 15 of each 28-day cycle in combination with daily oral sunitinib at 25 mg daily. During the first cycle of therapy, hemoglobin decreased to 10.0 g/dl, platelet count decreased to 113,000 per μl, neutrophil count decreased to 1,200 per μl, while creatinine remained stable at 1.82 μmol/l. A repeat CT in March 2007 (after 1 cycle) showed reduced paraesophageal, periaortic, gastrohepatic and retroperitoneal lymphadenopathy, and a decrease in the left pleural effusion (Figure 2B). The periaortic lymph node decreased from 2.9×2.0 cm to 1.9×1.1 cm.

Table I. Patient baseline characteristics and treatment regimens.

	Patient 1	Patient 2	Patient 3
Age at diagnosis (years)	64	51	64
Gender	Male	Female	Male
Initial diagnosis	Esophageal cancer	NSCLC adenosquamous	SCLC
EGFR receptor	Negative	Positive	Not tested
Smoking status	1 pack per day for 20 years; quit 30 years earlier	1 pack per day for 20 years	1-2 packs per day for 40 years
Previous therapies, n	1	6	4
Type	Cisplatin Irinotecan	Cisplatin Docetaxel Gemcitabine Pemetrexed Erlotinib Bevacizumab Carboplatin Alternative medications	Carboplatin Etoposide Epirubicin Irinotecan Cisplatin Bevacizumab Topotecan

NSCLC, Non-small cell lung cancer; SCLC, small cell lung cancer; EGFR, epidermal growth factor receptor.

During the second cycle of therapy, the hemoglobin nadir remained stable at 10.8 g/dl, platelet count decreased to 87,000 per μl and neutrophil count decreased to 900 per μl. The patient developed febrile neutropenia, received empiric antibiotics and recovered before the next cycle of therapy. The patients creatinine improved to 1.09 μmol/l. A CT performed on April 11, 2007 showed stable disease with a decrease in size of the periaortic lymph node to 1.1×1 cm. However, a head CT also performed on the same date showed that disease in the brain had progressed. Systemic chemotherapy treatment was stopped. The patient survived for another 5 months after receiving whole-brain radiation for multiple brain lesions before dying in September 2007.

Case 2

In 2005, a 51-year-old female with squamous cell carcinoma of the right upper lobe of the lung with metastases to the thoracic spine experienced stable disease after treatment with cisplatin 75 mg/m² and docetaxel 75 mg/m² for 2 cycles (Figure 1B). Because of subsequent hearing loss associated with cisplatin, the regimen was switched to gemcitabine 1,500 mg/m² and pemetrexed 500 mg/m² every 2 weeks as part of a clinical trial. The patient achieved a partial response after 6 cycles (per the study design) this treatment regimen was switched to docetaxel. After 2 cycles of treatment with docetaxel 75 mg/m², the patient experienced disease progression and

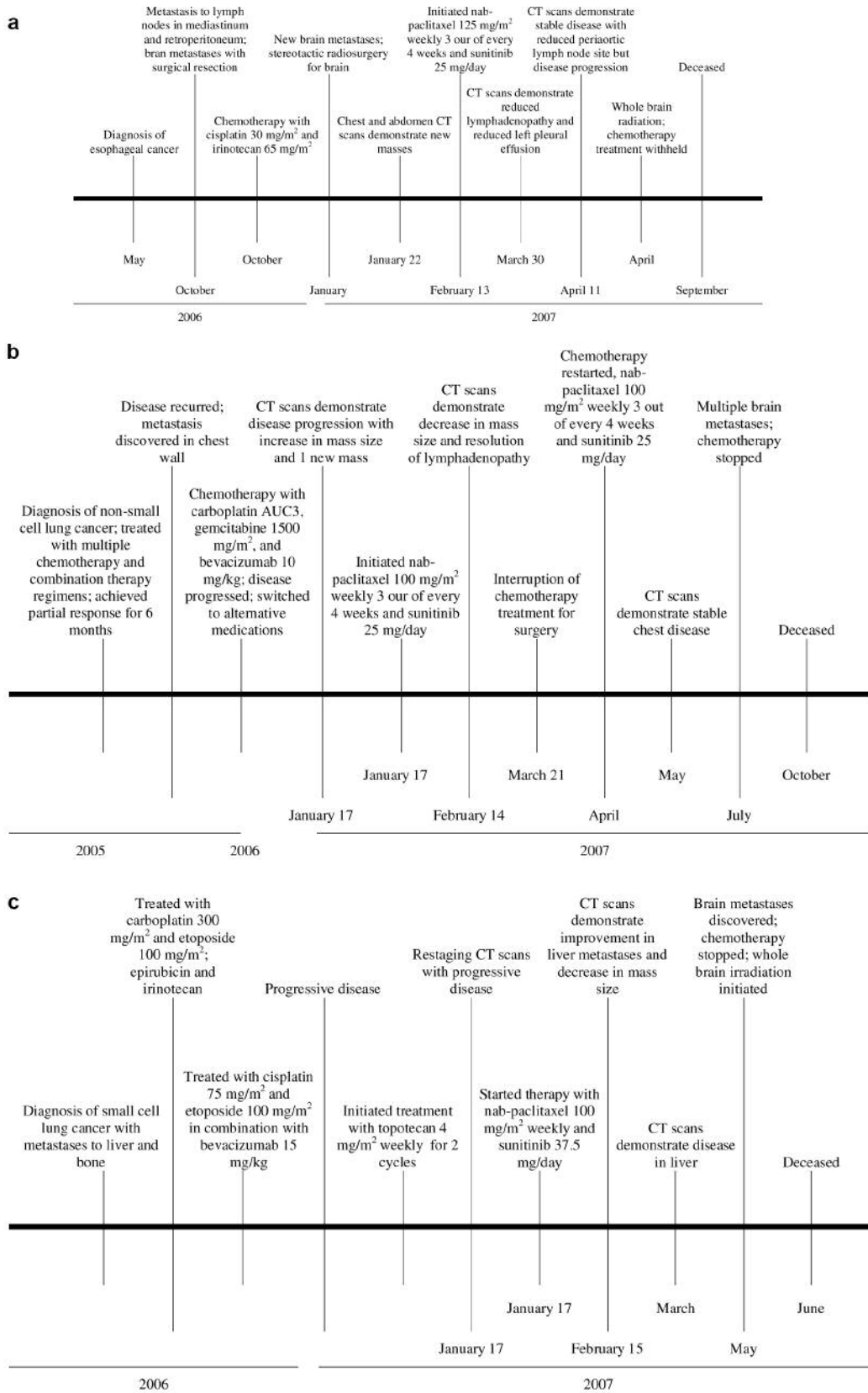


Figure 1. Patient history timelines for patients with A, esophageal cancer B, squamous cell carcinoma and C, small cell lung carcinoma.

the regimen was switched to pemetrexed 500 mg/m² monotherapy. However, the patient continued to experience disease progression after 2 cycles of this therapy. Treatment with erlotinib 150 mg orally and bevacizumab 10 mg/kg every 2 weeks was then started and the patient achieved a partial response for 6 months. Disease remained only in the right upper lobe. Unfortunately, during exploratory surgery, it was discovered that the mass was more centrally located, near the pulmonary artery branch. Therefore, a pneumonectomy was performed to control disease. Disease recurred 5 months later and a metastasis in the chest wall was discovered. The patient was treated with chemotherapy consisting of carboplatin area under curve (AUC) of 3, gemcitabine 1,500 mg/m² and bevacizumab 10 mg/kg every 2 weeks for 2 cycles, but she continued to experience disease progression.

The patient discontinued chemotherapy and started taking alternative medicines including walnut, warm wood, clove drops, red clover, blood root, galangal, sheep source tablet, L-arginine and mega-multivitamins. On presentation to the clinic in January 2007, she had pain in the right side of the chest wall because of the growing tumor and infection of skin and tumor tissue. Surgical incision was required to drain the subcutaneous abscess. Her physical examination was notable for tachycardia and an absence of breath sounds on auscultation of the right lung. Her electrolytes and liver function tests were normal with a white blood cell count of $14.5 \times 10^9/l$ and a platelet count of $511 \times 10^9/l$. A CT of the chest showed an increase in the size of masses in the right hemithorax and abdominal wall, new right axillary adenopathy, new multiple left lung nodules, increasing mass effect on the superior vena cava and central left brachiocephalic vein, and a new 1-cm nodule in the right pectoralis muscle (Figure 3A).

The patient then began treatment with the combination of nab-paclitaxel 100 mg/m² weekly $\times 3$ weeks of every 4-week cycle and sunitinib 25 mg orally daily. During the first cycle of therapy, hemoglobin remained stable at 12.0 g/dl, platelet count at 605,000 per μl and neutrophil count at 6,400 per μl . The patient returned to the clinic for follow-up examination and CT after 1 cycle of treatment. The 8 \times 10-cm mass in the right upper hemithorax extending into the anterolateral right chest wall had decreased to 5.8 \times 6.6 cm, the lymphadenopathy had resolved and the pleural nodule in the left upper lobe was unchanged (Figure 3B). There was a decrease in the size (to less than 1cm) and number of the lingular and left basilar nodules. A subcutaneous collection in the right flank decreased from 4.6 \times 3.6 cm to 3.8 \times 2.2 cm (Figure 3C and D). After the second cycle of chemotherapy, hemoglobin decreased to 8.9 g/dl, the platelet count decreased to 119,000 per μl and the neutrophil count decreased to 200 per μl . The patient received a subcutaneous injection of 480 μg of granulocyte colony-stimulating factor that resulted in a rapid neutrophil increase to

23,900 per μl within 1 week. Chemotherapy was stopped to allow for debridement of a surgical wound in the right thorax and placement of suction apparatus in the right chest wall.

At the end of April 2007, chemotherapy with nab-paclitaxel 100 mg/m² and daily oral sunitinib 25 mg was restarted. The hemoglobin count was 9.8 g/dl, the platelet count was 303,000 per μl and the neutrophil count had decreased to 1,700 per μl . At this cycle of therapy, hemoglobin remained stable at 9.5 g/dl, the platelet count was at 312,000 per μl , and the neutrophil count was 3,400 per μl throughout the cycle. The patient did not develop any nonhematological toxicities. Disease in the chest remained stable as evaluated by a CT in May 2007. In the last week of July, she presented to the local emergency room with facial twitching, and multiple brain metastases were discovered. Further chemotherapy was stopped and the patient received whole-brain radiation therapy. She died in October 2007.

Case 3

A 64-year-old male was diagnosed with SCLC with metastases to liver and bone (Figure 1C). He was initially treated with 2 cycles of carboplatin 300 mg/m² on day 1 and etoposide 100 mg/m² days 1 to 3, with a response in liver metastases. However, because of progression in bone, he was switched to epirubicin and irinotecan, then restarted cisplatin 75 mg/m² on day 1 and etoposide 100 mg/m² on days 1 to 3 in combination with bevacizumab 15 mg/kg. Progressive disease in the liver was identified, with a change in chemotherapy to weekly topotecan 4 mg/m² and consultation at the University of Minnesota to evaluate treatment options. The patient's only complaints were fatigue, tenderness in the right hand and depression. On examination, his vital signs were normal, there were no abnormalities on physical examination, and laboratory parameters were normal, except for a hemoglobin of 12.1 g/dl and a thyroid stimulator hormone (TSH) level of 8.19 mm/dl. The CT of the chest, abdomen, and pelvis, as compared with previous examinations, showed an increase in size of the right upper lobe mass, a decrease in size of some lung nodules, with an increase in others, and increasing size and number of hepatic metastases, with a 3.0 cm and 3.2 cm mass (Figure 4A). A right paratracheal lymph node was 1.5 cm compared with 1 cm, while a subcarinal lymph node decreased from 2.7 cm to 1.7 cm. There was a 4 \times 2.5 cm mass in the posterior right upper lobe that had increased from 2 \times 1.1 cm (Figure 4B). The patient received nab-paclitaxel 100 mg/m² on days 1, 8, and 15 of each 28-day cycle and oral daily sunitinib at 37.5 mg. During the first cycle of therapy, hemoglobin remained stable at 14.3 g/dl, platelet count decreased to 665,000 / μl and the neutrophil count was 7,200 per μl . A follow-up examination and CT after 1 cycle of therapy showed improvement in the

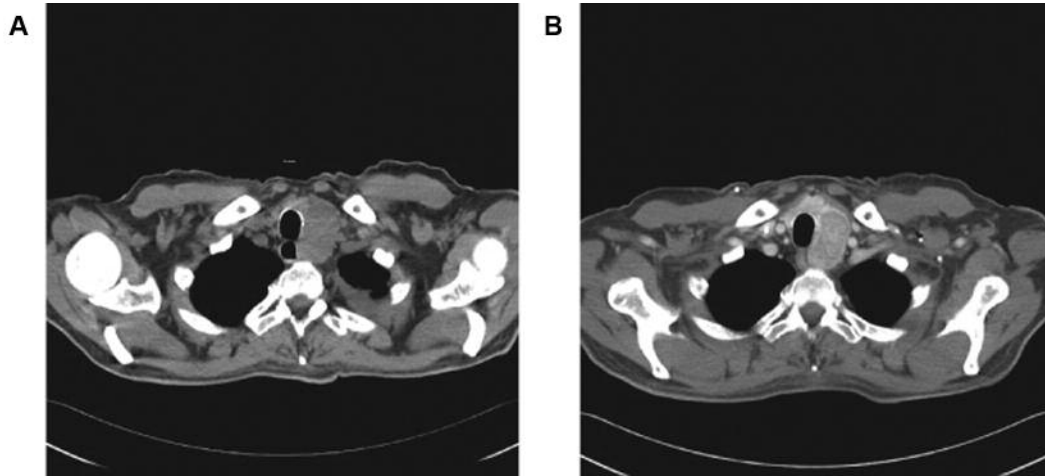


Figure 2. A 63-year-old man with esophageal cancer had a chest CT showing left pleural effusion with mediastinal and pulmonary window lymphadenopathy (A). After therapy with nab-paclitaxel and sunitinib, repeat CT showed reduced paraesophageal and periaortic lymphadenopathy with reduced left pleural effusion (B).

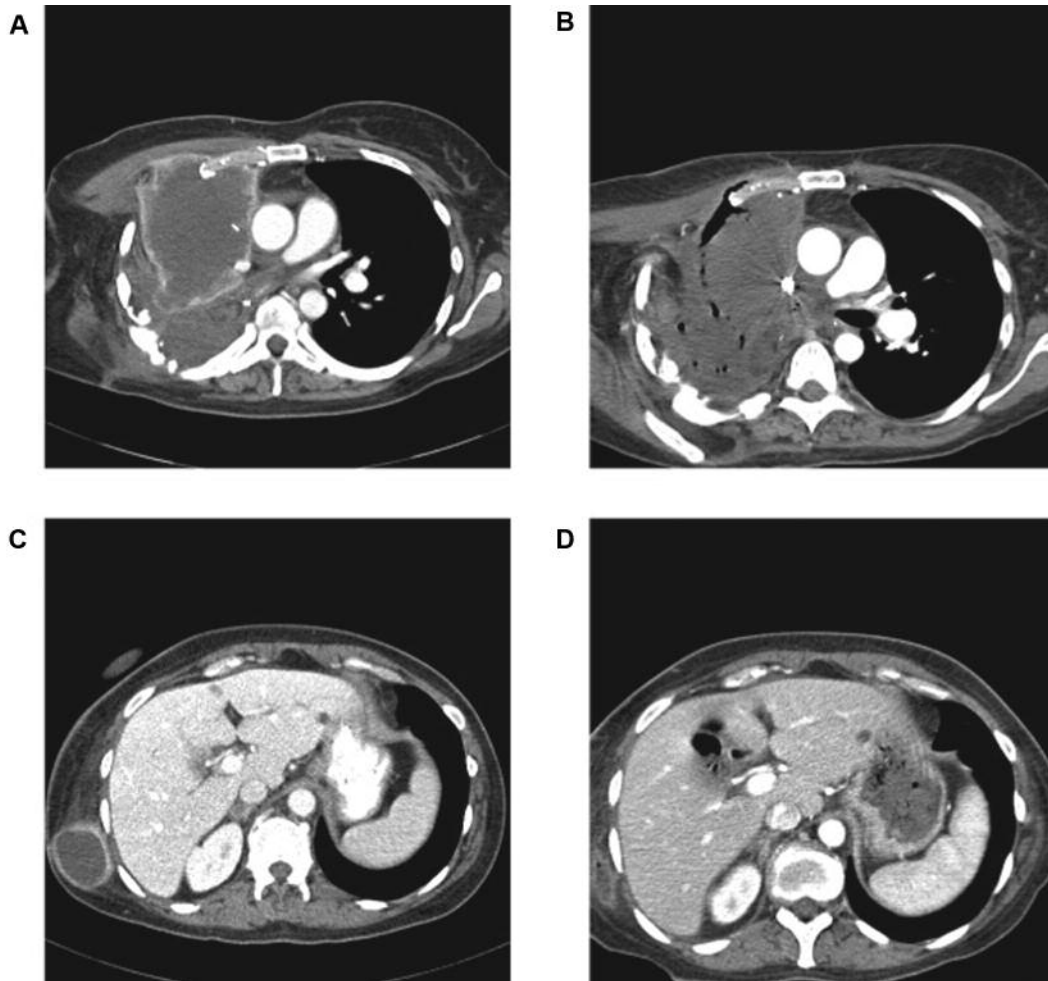


Figure 3. A 51-year-old woman with NSCLC had a CT showing tumor masses at several sites, including right hemithorax and abdominal wall (A). After 1 cycle of nab-paclitaxel and sunitinib, the right upper hemithorax mass (B) and a subcutaneous collection in the right flank (before therapy, C) significantly decreased in size (D).

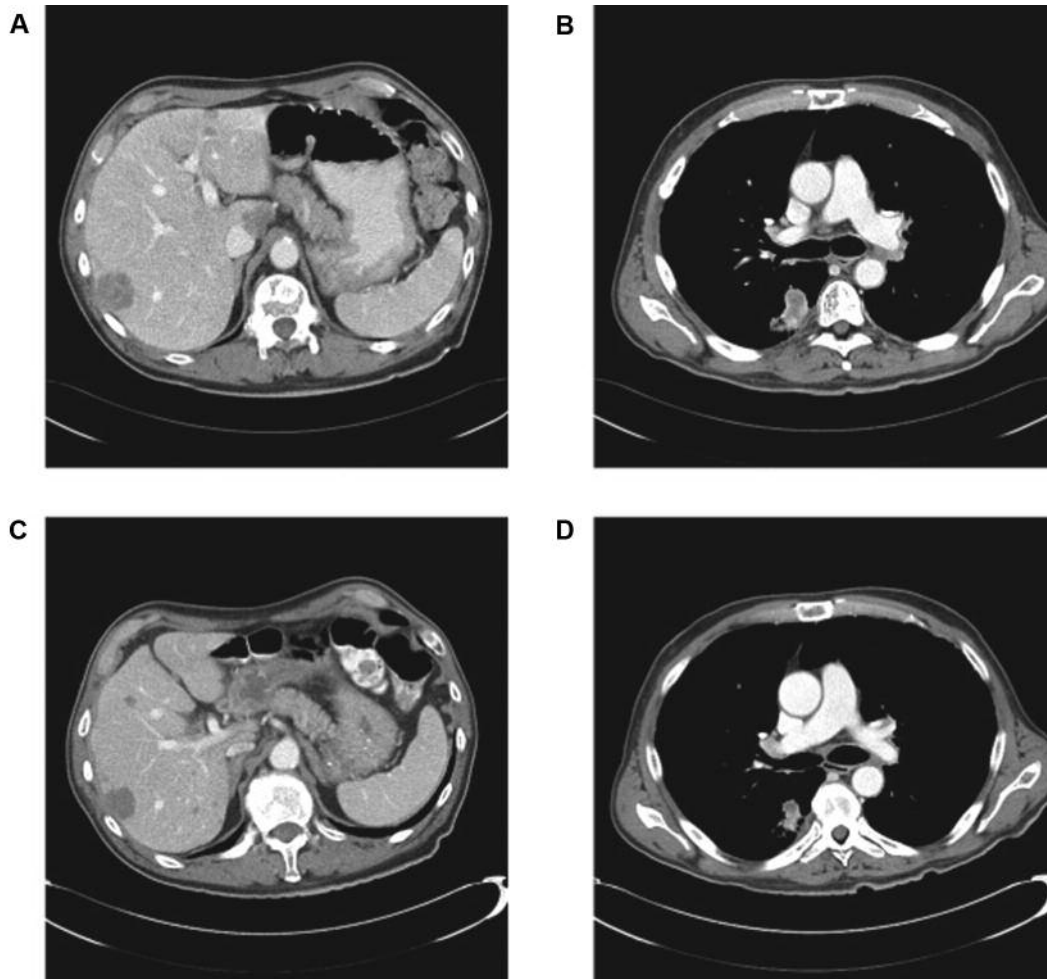


Figure 4. A 64-year-old man with SCLC had CT showing hepatic lesions (A). A mass was present in the posterior right upper lobe before treatment with nab-paclitaxel and sunitinib (B). The hepatic lesions decreased in size after treatment with nab-paclitaxel and sunitinib (C). The mass in the right upper lobe and satellite nodules decreased in size (D).

liver metastases, the right upper lobe mass, and right mediastinal and hilar adenopathy. The two largest liver lesions decreased in size to 2.3 cm and 2.5 cm (Figure 4C). The mass in the right upper lobe decreased to 2.6×2.0 cm, with a decrease in the size of the satellite nodules (Figure 4D). A right hilar lymph node that measured 1.8×3.6 cm before therapy decreased to 1.6×2.3 cm, but there was no change in numerous skeletal metastases.

After the second cycle of therapy, hemoglobin decreased to 9.8 g/dl, the platelet count was normal (255,000 per μl) and the neutrophil count was 3,600 per μl . The patient complained of fatigue and loss of appetite. A CT in March 2007 demonstrated disease progression in the liver. The patient insisted on further therapy; however, in May 2007, brain metastases were discovered and systemic chemotherapy was stopped. He received whole-brain radiation and died in June 2007.

Discussion

These three patient case reports demonstrate an improvement in disease state, with notable reduction of tumor size, and improvement in symptoms in patients treated with a combination regimen of nab-paclitaxel and sunitinib. In a patient with esophageal cancer, nab-paclitaxel and sunitinib treatment significantly decreased lymphadenopathy and pleural effusion. In a patient with NSCLC, the combination of nab-paclitaxel and sunitinib resulted in resolution of lymphadenopathy and reduced tumor mass and number. In a patient with SCLC, treatment improved liver metastases and significantly reduced tumor mass and adenopathy. This therapy was well tolerated with no grade 3 or 4 nonhematological toxicities.

Nab-paclitaxel is a novel, nanoparticle albumin-bound paclitaxel designed to increase the intratumoral concentration of the drug by a receptor-mediated transport process

allowing transcytosis across the endothelial cell wall. In a recent phase I/II trial of patients with NSCLC, nab-paclitaxel as first-line chemotherapy (125 mg/m² *i.v.* every 3 weeks) demonstrated significant tumor responses (overall response rate =38%) and a median survival of 10.3 months (9).

In these case studies, nab-paclitaxel was combined with sunitinib, a tyrosine kinase receptor inhibitor that is active against platelet-derived growth factor receptors, fibroblast growth factor receptors and vascular endothelial growth factor receptors. Sunitinib acts primarily by inhibiting angiogenesis and tumor growth. In a recent phase II trial, patients with NSCLC treated with sunitinib (37.5 mg/day daily for 4 weeks) experienced median progression-free survival of 12 weeks and the treatment was generally well tolerated (14). Additionally, sunitinib (37.5 mg or 50.0 mg/day) in combination with gemcitabine and cisplatin was well tolerated in patients with advanced NSCLC (15).

Combination therapy with nab-paclitaxel and sunitinib was shown to be safe and efficacious in metastatic esophageal, NSCLC and SCLC. Based on the apparent efficacy of the regimen of nab-paclitaxel and daily sunitinib and easily managed toxicities in these previously chemotherapy treated patients, phase II clinical trials assessing the efficacy of this combination therapy for treatment of advanced thoracic cancer are warranted.

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