

## Congestive Heart Failure Secondary to Gemcitabine Nab-paclitaxel in Patients with Pancreatic Cancer

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**Abstract.** *Background: Gemcitabine plus nab-paclitaxel is a novel combination chemotherapy that is currently being used in patients with metastatic pancreatic cancer. Phase III trials have shown improved survival, response rates, and disease-free progression. The most significant side-effects include peripheral neuropathy and myelotoxicity. Review of literature has shown rare cases of congestive heart failure associated with gemcitabine plus nab-paclitaxel. We describe two cases of women who were treated with gemcitabine plus nab-paclitaxel for pancreatic adenocarcinoma who developed acute exacerbation of congestive heart failure. Patients and Methods: Two women with pancreatic adenocarcinoma were both treated with gemcitabine plus nab-paclitaxel and developed acute decompensated heart failure requiring hospitalization and standard treatment for heart failure including i.v. diuretics. Once chemotherapy was discontinued, symptoms resolved. Conclusion: Based on review of literature, as far as we are aware of, this is the first report of congestive heart failure as an adverse effect of combination therapy. Both patients had evidence of diastolic dysfunction which may have predisposed them to cardiac toxicity secondary to gemcitabine plus nab-paclitaxel. The exact mechanism of action is currently unknown and requires further studies. However, it is imperative for physicians to be aware of this adverse effect and closely monitor patients with underlying heart disease who are undergoing treatment with gemcitabine plus nab-paclitaxel.*

Pancreatic cancer is one of the most fatal types of cancer, with survival rates of about 26% at one year and about 6% at five

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years. It is the tenth most common cancer diagnosed in the US and the fourth most common cause of cancer-related deaths. About 52% of patients are found to have metastatic disease at diagnosis, which leads to an approximate median survival of six months (1). Gemcitabine is the first-line treatment for locally advanced and metastatic pancreatic cancer, with an associated median survival of about 5.7 months (2).

Nab-paclitaxel, a 130-nm particle made of paclitaxel bound to albumin, has been shown to have antitumor activity (2). Paclitaxel is a microtubule-targeting agent that can cause cardiac complications, most commonly hypotension, which occurred in about 5% of patients in the first three hours of infusion (3). Other cardiac complications include sinus bradycardia, ventricular ectopy, tachycardia, atrioventricular block, bundle branch block, thrombosis and, rarely, cardiac ischemia (4). Congestive heart failure was reported in patients who had received paclitaxel in combination with doxorubicin. It has been suggested that paclitaxel increases plasma levels of doxorubicin, which can cause congestive heart failure (3).

Gemcitabine is a nucleoside analog, with the most common adverse effects of its use being myelosuppression, elevated liver enzymes, edema, and dyspnea. In regards to cardiac complications, gemcitabine is associated with venous thromboembolisms, acute arterial events, systemic capillary leak syndrome, digital ischemia or necrosis, vasculitis and thrombotic microangiopathy (4).

A recent phase III trial was performed to study the efficacy and safety of the combination of nab-paclitaxel and gemcitabine in patients with metastatic pancreatic cancer. The present study showed a median overall survival of 8.5 months in the combination group compared to 6.7 months in the gemcitabine group, which was statistically significant. The study also showed improved progression-free survival and response rates. The most common grade 3 adverse effects of nab-paclitaxel plus gemcitabine were neutropenia, fatigue, and peripheral neuropathy (5). Common adverse events of nab-paclitaxel and gemcitabine are listed in Table I.

Acute congestive heart failure is a life-threatening adverse effect that has been rarely associated with gemcitabine or

Table I. Common adverse events of nab-paclitaxel plus gemcitabine compared to gemcitabine alone. Adapted from Von Hoff et al., 2013 (5).

Adverse event	Nab-Paclitaxel plus gemcitabine (N=421) (%)	Gemcitabine alone (N=402) (%)
Death	18 (4)	18 (4)
Grade $\geq 3$ hematological adverse event		
Neutropenia	153/405 (38)	103/388 (27)
Leukopenia	124/405 (31)	63/388 (16)
Thrombocytopenia	52/405 (13)	36/388 (9)
Anemia	53/405 (13)	48/388 (12)
Febrile neutropenia	14 (3)	6 (1)
Grade $\geq 3$ non-hematological adverse event occurring in $>5\%$ of patients		
Fatigue	70 (17)	27 (7)
Peripheral neuropathy	70 (17)	3 (1)
Diarrhea	24 (6)	3 (1)

nab-paclitaxel. We describe two cases of women with pancreatic cancer who underwent treatment with gemcitabine plus nab-paclitaxel and developed acute exacerbation of congestive heart failure that persisted even with single-agent gemcitabine.

### Case Reports

*Case 1.* A 77-year-old female with a past medical history including coronary artery disease status post coronary artery bypass grafting, atrial fibrillation, chronic diastolic heart failure, hyperlipidemia, hypertension, and type 2 diabetes mellitus had recently been diagnosed with pancreatic adenocarcinoma. She presented with complaints of weight loss and diarrhea. She underwent magnetic resonance cholangiopancreatography which showed an enlarging mass in the pancreatic head with encasement of the superior mesenteric vein and abutting the superior mesenteric artery. She underwent surgical biopsy of the pancreatic head, which demonstrated pathology of mucinous adenocarcinoma. Therapy was initiated with gemcitabine (1,000 mg/m<sup>2</sup> days 1, 8 and 15) and nab-paclitaxel (125 mg/m<sup>2</sup> days 1, 8 and 15) on a 28-day cycle for treatment of locally advanced pancreatic cancer. Completion of treatment was limited by side-effects including rash, anemia, gastrointestinal bleed, thrombocytopenia, and acute congestive heart failure. She was only able to complete three partial cycles of gemcitabine plus nab-paclitaxel. About 10 days after her last dose of gemcitabine plus nab-paclitaxel, on 10/2/2013, she had fever and chills. She was hospitalized for treatment of pneumonia given chest x-ray findings. She was then transferred to Tufts Medical Center where her primary oncologist was located. She complained of shortness of breath. Chest x-ray showed diffuse

increased linear opacities consistent with interstitial pulmonary edema and bilateral pleural effusions. Echocardiography at this time showed a normal ejection fraction of 65%. She was treated with *i.v.* furosemide with improvement in symptoms and was discharged on a higher dose of furosemide. The chemotherapy regimen was changed to single agent gemcitabine (1,900 mg/m<sup>2</sup>) given the exacerbation of acute congestive heart failure after gemcitabine plus nab-paclitaxel. After five cycles of gemcitabine, she had an acute exacerbation of congestive heart failure requiring hospitalization and treatment with *i.v.* furosemide drip and metolazone. The echocardiography at this time showed an ejection fraction of 65% with abnormal diastolic parameters. At this point, it was decided to stop gemcitabine completely and initiate therapy with 5-fluorouracil (5-FU; 500 mg/m<sup>2</sup>) and leucovorin (500 mg/m<sup>2</sup>). The patient has been tolerating this regimen very well with no signs or symptoms of exacerbation of congestive heart failure until this point. Please refer to Figure 1 for timeline of symptoms.

*Case 2.* A 66-year-old female with past medical history significant for hepatitis C, type 2 diabetes mellitus, and significant smoking history presented with painless jaundice, a 6.8 kg of weight loss, and dyspepsia. Subsequent evaluation revealed a mass in the head of the pancreas; she underwent Whipple's procedure with surgical pathology revealing mucinous invasive carcinoma. The tumor size was 1.5 cm  $\times$  1.5 cm  $\times$  1.5 cm and had locally invaded the peripancreatic retroperitoneal soft tissue. One out of two lymph nodes were disease-positive. The pathological stage of the tumor was pT3pN1pMx consistent with stage IIIB pancreatic cancer. After surgery, she received four cycles of adjuvant gemcitabine (1,000 mg/m<sup>2</sup>). Therapy of 5-FU

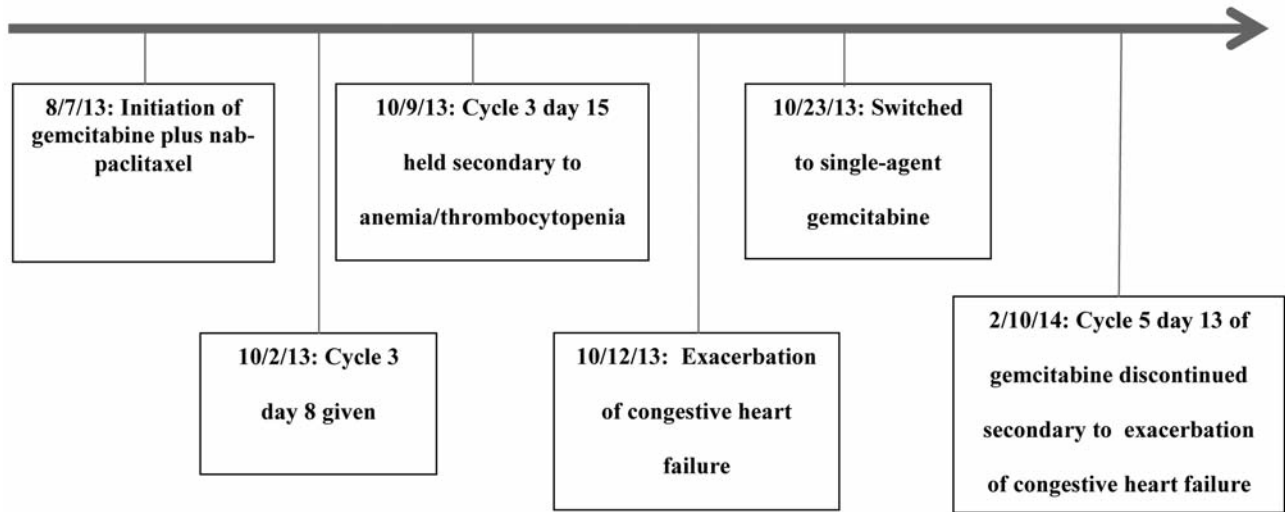


Figure 1. Timeline of acute congestive heart failure after gemcitabine plus nab-paclitaxel in case 1.

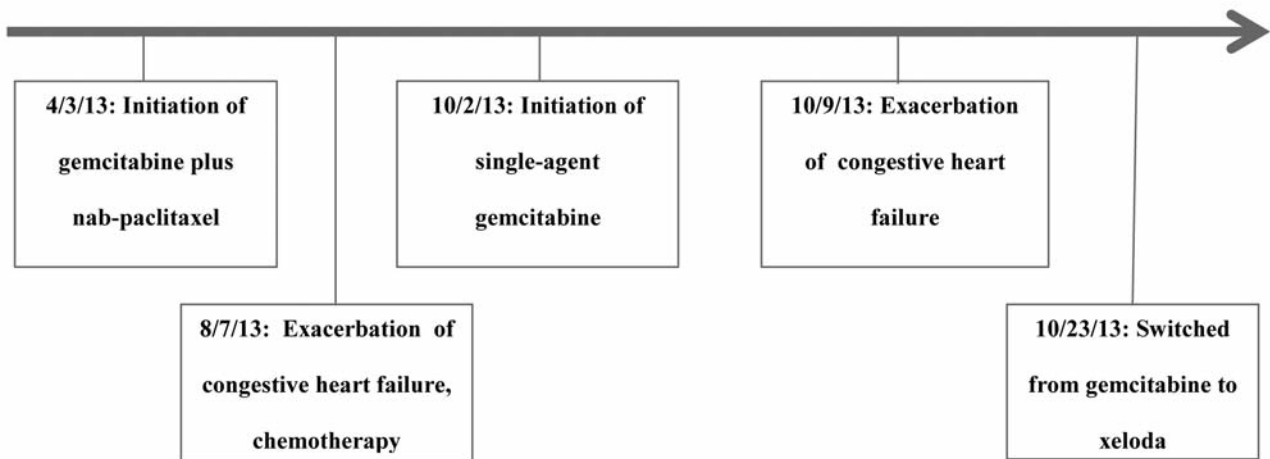


Figure 2. Timeline of acute congestive heart failure after gemcitabine plus nab-paclitaxel in case 2.

(500 mg/m<sup>2</sup>/d) with concurrent radiation therapy (4/2008) was attempted, but this was not tolerated due to abdominal wall infection. She was eventually found to have biopsy-proven metastases to the lung. She underwent video-assisted thoracic surgery and wedge resection of the left lower lobe. She was found to have visceral pleural extension in the fissure and chest wall. She completed 12 cycles of FOLFOX 6 at a standard dose. She was then found to have an increase in size and number of pulmonary nodules. The patient was then switched to gemcitabine (1,000 mg/m<sup>2</sup>) plus nab-paclitaxel (125 mg/m<sup>2</sup>) with improvement in nodule size. However, after five cycles of this therapy, she developed acute decompensated heart failure requiring hospitalization.

Gemcitabine plus nab-paclitaxel was then switched to gemcitabine alone (1,000 mg/m<sup>2</sup>) days 1 and 8 of a 21-day cycle. However, after one cycle of gemcitabine, she presented to the hospital with 8 kg weight gain, dyspnea, and lower extremity edema consistent with acute congestive diastolic heart failure. Echocardiography showed an ejection fraction of 60% with trans-mitral spectral Doppler flow pattern suggestive of abnormal diastolic dysfunction. She was treated with *i.v.* furosemide and her home regimen of furosemide was increased on discharge. Gemcitabine was discontinued and she was switched to capecitabine (1,000 mg/m<sup>2</sup>) with no new exacerbations of congestive heart failure. Please refer to Figure 2 for timeline of symptoms.

## Discussion

This report describes two cases of patients who developed acute exacerbation of congestive heart failure after treatment with gemcitabine plus nab-paclitaxel and gemcitabine alone. The introduction of novel chemotherapeutic agents has significantly improved survival rates for many cancer types. Simultaneously, adverse effects of the chemotherapeutic agents are being discovered as more patients undergo new therapies. Cardiotoxicity is a life-threatening complication. Cases of congestive heart failure secondary to gemcitabine or nab-paclitaxel are rare in the literature. There have been few cases of congestive heart failure and left ventricular dysfunction seen in patients undergoing treatment with nab-paclitaxel alone, which are reported on the Celgene website. However, most patients had underlying cardiac disease or had been previously exposed to cardiotoxic drugs (3). The first patient reported herein had a significant underlying cardiac history which likely predisposed her to developing recurrent exacerbations while on gemcitabine plus nab-paclitaxel. The exact mechanism of this toxicity is unclear. However, murine studies have shown that nab-paclitaxel in combination with gemcitabine has synergistic activity, improving the intra-tumoral concentration of gemcitabine, which would also increase toxicity (5).

Paclitaxel-alone has been shown to cause various cardiac disturbances, most commonly sinus bradycardia, which occurred in about 29% of patients in phase II trials (2). As mentioned before, arrhythmias may occur and rarely ischemia (2). Gemcitabine alone has been shown to have few cardiac effects, including stroke, arrhythmias and hypertension. About 2% of patients discontinued treatment secondary to cardiovascular adverse events during clinical trials. In post-marketing experience, congestive heart failure and myocardial infarction have rarely been reported (3). A small retrospective study of 156 patients in 2013 reported new-onset congestive heart failure in about 4.5% of patients undergoing treatment with gemcitabine compared to 0.76% which has been reported in previous studies. It was found that these patients did have a history of underlying cardiac disease. It was also noted that these patients were treated with a dose in excess of 17,000 mg/m<sup>2</sup> (6).

To our knowledge, these are the first cases reported in the literature of acute exacerbation of congestive heart failure secondary to gemcitabine plus nab-paclitaxel. Greater understanding of the mechanisms by which this combination leads to heart failure is critical. Further studies need to be performed in this area in order to better manage this adverse effect. It is imperative for patients who develop acute exacerbation of congestive heart failure to be treated with the standard medical management for heart failure, including diuretics along with discontinuation of gemcitabine plus nab-paclitaxel. When initiating this combination in patients with metastatic pancreatic cancer, one must consider closer monitoring for those with underlying cardiac disease, or possibly consider other alternatives (4).

## References

- 1 Tarver T: Cancer Facts & Figures 2012. American Cancer Society (ACS). Journal of Consumer Health On the Internet 16(3): 366-367, 2012.
- 2 Von Hoff D, Ramanathan R, Borad M, Laheru D, Smith L, Wood T, Korn R, Desai N, Trieu V, Iglesias J, Zhang H, Soon-Shiong P, Shi T, Rajeshkumar N, Maitra A and Hidalgo M: Gemcitabine plus Nab-paclitaxel Is an Active Regimen in Patients with Advanced Pancreatic Cancer: A Phase I/II Trial. J Clin Oncol 29.34: 4548-554, 2011.
- 3 Abraxane Prescribing Information. Abraxane Celgene Corporation 2013. Web. 01 July. 2014. <<http://abraxane.com/wp-content/pi/prescribing-info.html>>.
- 4 Senkus E and Jassem J: Cardiovascular Effects of Systemic Cancer Treatment. Cancer Treat Rev 37.4: 300-311, 2011.
- 5 Von Hoff D, Ervin T, Arena F, Chiorean E, Infante J, Moore M, Seay T, Tjulandin S, Ma W, Saleh M, Harris M, Reni M, Dowden S, Laheru D, Bahary N, Ramanathan R, Tabernero J, Hidalgo M, Goldstein D, Van Cutsem E, Wei X, Iglesias J, and Renschler M: Increased Survival in Pancreatic Cancer with Nab-paclitaxel plus Gemcitabine. New Engl J Med 369(18): 1691-1703, 2013.
- 6 Shrum K, Gill S, Thompson L, Blackhurst D, Puls L: New-onset Congestive Heart Failure with Gemcitabine in Ovarian and Other Solid Cancers. Amer J Clin Oncol 37(4): 364-368, 2014.

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