Unexpected outcome (positive or negative) including adverse drug reactions

BOOP as a rare complication of gemcitabine therapy

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Summary

Gemcitabine is commonly used in combination with carboplatin in patients with advanced non-small-cell lung cancer (NSCLC). Gemcitabine has good clinical activity against NSCLC and is well tolerated by the patients. Myelosuppression is its dose-limiting toxicity. A potential side effect of gemcitabine is pulmonary toxicity. Among pulmonary toxicities, pneumonia, bronchospasm, acute respiratory distress syndrome, pleural effusion and interstitial pneumonitis are well documented, but bronchiolitis obliterans organising pneumonia (BOOP) is a rarely observed adverse effect of gemcitabine therapy. The authors report a female patient who presented with progressively worsening shortness of breath, low-grade fever and non-productive cough 10 days after completion of gemcitabine therapy for poorly differentiated invasive squamous cell carcinoma of lung with bone metastases. Histopathology of a transbronchial biopsy established the diagnosis of BOOP. Treatment with intravenous steroids resulted in prompt clinical improvement, but the patient later died of progression of her lung cancer.

BACKGROUND

In 1985, Epler *et al* described bronchiolitis obliterans organising pneumonia (BOOP), also known as cryptogenic

organising pneumonia (COP), as a distinct disorder of lungs characterised by 'polypliod endobronchial connective tissue masses composed of mixed fibroblasts resembling

Figure 1 A CT scan of thorax with contrast showing scattered bilateral ground-glass opacities throughout the lung parenchyma.

Figure 2 Bronchoscopic biopsy specimen of the left lung showing lung parenchyma with granulomatous inflammation.

Figure 3 A CT scan of thorax with contrast showing bilateral resolution of ground-glass opacities throughout the lung parenchyma.

Table 1 Summary of case reports of BOOPs in association with gemcitabine therapy

Primary diagnosis	Treatment for malignancy	Presentation	Imaging studies	Blood culture/ serology/ histopathology	Antimicrobial treatment	Steroid therapy	Ref
61-Year-old male, 40 pack/year history of smoking	Taxotere and gemcitabine	Dyspnoea, low grade fever, tachypnoea, cyanosis, tachycardia, disseminated crackles, hypoxaemia requiring oxygen	CXR: alveolar infiltrates bilaterally, CT chest: multiple patchy alveolar opacities varying from areas of ground glass density or consolidation and a diffuse parenchymal infiltration	Negative/negative for <i>Legionella</i> , <i>Mycoplasma</i> , <i>Coxiella</i> , <i>Chlamydia</i> , adenovirus, cytomegalovirus and influenza A virus/not reported	Cefepime, clarithromycin and levofloxacin with no clinical or radiological evidence of improvement	Methylprednisone, significant clinical improvement and disappearance of alveolar infiltrate in repeat chest CT	11
69-Year-old female, no smoking history mentioned	Paclitaxel, carboplatin, gemcitabine	Dry cough, dyspnoea, asthenia, fever, and hypoxaemia requiring oxygen	CXR: bilateral interstitial infiltrates, CT chest: bilateral interstitial infiltrate predominating in the right lung and patches of ground-glass attenuation	Not reported/negative for <i>Legionella</i> , <i>Mycoplasma</i> , <i>Coxiella</i> , <i>Chlamydia</i> , adenovirus, cytomegalovirus and influenza A virus/consistent with BOOP on examination of transbronchial biopsy	Not reported	Corticosteroid, rapid clinical improvement within 24 h. Complete resolution of lung infiltrates in repeat CXR after 21 days	12

BAC, bronchoalveolar carcinoma; BOOP, bronchiolitis obliterans organising pneumonia; CXR, chest x-ray.

granulation tissue filling the lumens of terminal and respiratory bronchioles and extending in a continuous fashion into alveolar ducts and alveoli, representing an organising pneumonia'.¹ It usually presents as low-grade fever, non-productive cough, malaise, dyspnoea, anorexia and weight loss.²⁻⁴ Distinct pathological, clinical and radiological findings are required to diagnose BOOP. The imaging studies are very characteristic and typical cases consists of multiple patchy alveolar opacities with peripheral and bilateral distribution. The size of opacities varies in size from a few centimetres to a whole lobe, and the density varies from ground glass to consolidation.⁵ Histological examination of lung biopsy specimens shows intra-alveolar buds of granulation tissue consisting of fibroblasts, myelofibroblasts and loose connective tissue, and if bronchiolar lesions are present, they show similar buds of granulation tissue inside the airway lumen.⁵ Usually erythrocyte sedimentation rate and C reactive protein levels are increased with leucocytosis and neutrophilia. Early diagnosis is important because most of the time the disease can effectively be treated with corticosteroids.

Here we present a rare case of BOOP following treatment with gemcitabine for metastatic non-small-cell lung cancer (NSCLC).

CASE PRESENTATION

A Caucasian female in her mid-50s with medical history significant for hepatitis C virus infection and 40 pack/year history of smoking, presented to our hospital with right shoulder and back pain a few days after she slipped on ice. She denied shortness of breath, cough, sputum production, haemoptysis, fever or chills. She reported loss of appetite and had lost 20 pounds of weight over the preceding months. She also denied paresthesia or weakness in her extremities and did not report of incontinence. Her findings on physical examination and laboratory studies were unremarkable. Imaging studies revealed fracture of the surgical neck of the right humerus and a compression fracture of the T11 vertebra. A CT of spine and chest was obtained which revealed destructive osteolytic changes of T11 vertebrae, a right suprahilar mass with obstruction of right upper lobe bronchus and mediastinal adenopathy. A bronchoscopy with biopsy of the right upper lobe bronchus and transbronchial aspiration of the right paratracheal lymph node was performed. Biopsy revealed poorly differentiated invasive squamous cell carcinoma of lung. A positron emission tomography scan showed uptake in the lung as well as the T11 vertebra. An MRI of the brain showed no evidence of brain metastases. The patient received dexamethasone intravenously (4 mg, q8h) and her pain significantly improved. She was treated with radiation therapy, and following completion of radiotherapy, she was commenced on palliative chemotherapy with carboplatin (on day 1) at an area under curve 5 and gemcitabine (Gemzar) 1000 mg/m² on days 1 and 8, every 3 weeks for four cycles. The patient also received zoledronic acid, 4 mg intravenous every 3 weeks.

The patient received two treatments of gemcitabine after which she experienced difficulty in breathing. Ten days postchemotherapy she experienced severe exertional dyspnoea and was readmitted. She was hypoxic and required oxygen via nasal cannula to maintain oxygen saturation >92%. She reported low-grade fever and

non-productive cough, but denied sweats, chills, nausea, vomiting or diarrhoea. She did not report recent travel. Her white cell count gradually increased up to $20.32 \times 10^4/\text{ml}$ of blood, and her chemistry panel showed severe hypoalbuminemia and transaminase elevation (aspartate transaminase $226 \mu\text{l}$, alanine transaminase $223 \mu\text{l}$) and alkaline phosphatase $136 \mu\text{l}$. A chest x-ray showed extensive bilateral interstitial infiltrates which were not present during her prior admission. CT scan of chest showed diffuse ground-glass interstitial infiltrates throughout the lung parenchyma sparing the right upper lobe, and decrease size of the right upper lobe lung mass. A repeat CT chest done 1 week later showed diffuse increased marked ground-glass opacities bilaterally (figure 1, arrow). Her blood cultures were negative. Her urine was positive for *Streptococcus pneumoniae* antigen. She was not a *Staphylococcus aureus* nasal carrier. Staining and culture of her respiratory secretions were negative. She was empirically treated with ceftriaxone, vancomycin and azithromycin without clinical improvement of her breathing. She underwent bronchoscopy for bronchoalveolar lavage and transbronchial biopsy. The latter showed lung parenchyma with granulomatous inflammation (figure 2, arrow) and focal fibroblastic (BOOP-like) reaction, and special stains of biopsied tissues for acid fast bacilli, *Pneumocystis jiroveci* and fungal organisms were negative. Viral inclusions were not identified in the biopsy sample. Antibiotic therapy was discontinued and patient was started on intravenous steroids. The patient's condition quickly improved, and she was weaned off oxygen therapy. A CT scan of chest showed disappearance of alveolar infiltrates and resolution of consolidation (figure 3). Her lung cancer slowly progressed and she died.

DISCUSSION

ASCO guidelines recommend use of platinum based doublets with drugs such as gemcitabine as the preferred combination for patients with advanced NSCLC.⁶ Preclinical studies have demonstrated synergistic interaction between gemcitabine and cisplatin, and good clinical activity against NSCLC.⁷ Although cisplatin is generally the favoured platinum agent, carboplatin is often used with gemcitabine because of convenience of use and favourable toxicity profile.⁸ Gemcitabine is a pyrimidine antimetabolite and incorporates its active nucleotide metabolite into DNA resulting in chain termination and inhibition of DNA synthesis.⁹ Gemcitabine has been used as a standard for the adjuvant and metastatic treatment of a wide variety of malignancies including breast, ovary, pancreas, bladder and NSCLC. It is a relatively well tolerated drug but myelosuppression is its dose-limiting toxicity.¹⁰ Although pulmonary toxicities including pneumonia, capillary leak syndrome, bronchospasm, acute respiratory distress syndrome, pleural effusion and interstitial pneumonitis due to gemcitabine use has been reported,¹⁰ only two cases of BOOP have been reported to date

(table 1).^{11 12} A literature search for carboplatin-related BOOP yielded no reports.

BOOP may be idiopathic (COP) or secondary to various underlying conditions. Infectious causes of BOOP include *Chlamydia pneumoniae*, *Mycoplasma pneumoniae*, *Legionella pneumophila*, *Nocardia asteroides*, *S pneumoniae*, *S aureus*, herpes virus, HIV, adenovirus, parainfluenza and influenza virus, *Cryptococcus neoformans*, *P jiroveci* and malaria parasite.¹ Among different drugs reported to be associated with BOOP are bleomycin, amiodarone, phenytoin, fluoxetine, minocycline, sulfasalazine, ticlopidine, cephalosporin, amphotericin, carbamazepine etc. BOOP has also been reported in association with dermatomyositis, polymyalgia rheumatica, ankylosing spondylitis, Behcet's disease, common variable immunodeficiency disease and mixed cryoglobulinemia among many other associated diseases/conditions reported.¹ Generally, immunocompromised patients are not known to be at increased risk of developing BOOP. BOOP usually presents as viral-like illness with low-grade fever, cough and dyspnoea. Clinically, the symptoms can be similar to interstitial pneumonitis. In one study, interstitial pneumonitis was distinguished from BOOP on the basis of features on chest radiographs; the most characteristic radiologic finding in BOOP was the presence of the patchy areas of airspace consolidation.¹³ In high resolution CT, traction bronchiectasis and interlobular septal thickening are more common in interstitial pneumonitis than BOOP. Lung parenchymal nodules and peripheral distribution are more common in BOOP than interstitial pneumonitis. Pulmonary function testing shows decreased vital capacity and normal flow rate in both interstitial pneumonitis and BOOP. Antibiotic treatment does not cause significant clinical or radiographic improvement raising the suspicion of BOOP, and prompt corticosteroid therapy results in rapid improvement of the condition.¹ To confirm an association between a drug and BOOP, other causes, especially infectious causes must be ruled out. Lung biopsy remains the preferred method to establish the diagnosis, and microbiological, cytological and histopathological examination should be carried out to confirm the diagnosis of BOOP.

When a patient undergoing gemcitabine chemotherapy presents with acute onset of dyspnea, appropriate investigation for pneumonia should be initiated. Microbiological examination of appropriate specimens, blood culture and serology should be obtained. If those tests are negative and no clinical improvement is achieved with antimicrobial therapy, a diagnosis of BOOP should be considered. High resolution CT scan of the chest and transbronchial biopsy will aid in establishing the definitive diagnosis. Corticosteroid (prednisone or methylprednisolone) is the treatment of choice for BOOP. Though inhaled triamcinolone has been successfully used in treatment of BOOP,¹⁴ accepted treatment is prednisone at a dose between 0.75 and 1.50 mg/kg/day for the first 1–3 months and then tapered over 3–12 months according to response and clinical improvement.

Learning points

- ▶ BOOP or COP is a distinct disorder of lungs that can clinically present as pneumonia.
- ▶ Histology of lungs shows intra-alveolar buds of granulation tissue consisting of fibroblasts, myelofibroblasts and loose connective tissue, and if bronchiolar lesions are present, they show similar buds of granulation tissue inside the airway lumen.
- ▶ Gemcitabine can cause BOOP and only two cases of BOOP have been reported to date. To confirm an association between a drug and BOOP, other causes, especially infectious causes must be ruled out.
- ▶ Once the diagnosis of BOOP is confirmed, early intervention including withdrawal of the chemotherapeutic agent and prompt use of corticosteroids is recommended.

Competing interests None.

Patient consent Not obtained.

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