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Case Study

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THALIDOMIDE AND BORTEZOMIB INDUCED INTERSTITIAL PNEUMONITIS IN PATIENT WITH MUTIPLE MYELOMA

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ABSTRACT

Long term use of the combination of the thalidomide and bortezomib is associated with the risk of interstitial pneumonia in individuals with the multiple myeloma. Here is the case of the 48years old male who has the history of the multiple myeloma since 4 ½ years and was on chemotherapy with thalidomide and bortezomib since 4years. Patient has the history of the bronchial asthma since childhood and uses inhaler occasionally. Complaints of shortness of breath(grade-iv), cough since 1year.

KEYWORDS: Interstitial pneumonitis, thalidomide, bortezomib, multiple myeloma.

INTRODUCTION

Multiple myeloma (MM) is a clonal disorder of malignant plasma cells that comprises approximately 10% of hematologic malignancies.[1] Treatment of the disease consists of chemotherapy, antiangiogenic agents, immunomodulators, and autologous stem cell transplants.[2] Bortezomib, an inhibitor of 26 proteasome, is recently approved treatment option for MM. Thalidomide has anti-angiogenic and immunomodulatory effects. Recently, it has been used increasingly worldwide as a first-line and salvage therapy for multiple myeloma.[3]

The reported common adverse effects of bortezomib and thalidomide are asthenic conditions, GI disturbances, peripheral neuropathy and pulmonary complications are believed to be uncommon, interstitial lung disease is rare.[4] The different causes of interstitial pneumonitis can be classified into following 4 categories.

1. Diseases associated with a condition that affects other parts of the body (for ex: autoimmune diseases)
2. Disease associated with a specific exposure to an agent known to damage the lungs (for example, medications, occupational exposure etc.)
3. Diseases associated with known genetic abnormalities (for example, Hermansky-pudlak syndrome) and
4. Idiopathic diseases (diseases of unknown cause).[5]

CLINICAL PRESENTATION

The clinical presentation of the Interstitial pneumonitis varies based on the severity. The general symptoms include cough (can be chronic or dry), fatigue or inability to exercise, shortness of breath or fast breathing and deformity of nails, weight loss. Other common symptoms include sweats, chills, rigors, chest discomfort, pleurisy, haemoptysis, fatigue, myalgia's, anorexia, headache, and abdominal pain.

Common physical findings include fever (or) hypothermia, tachypnea, tachycardia and arterial oxygen saturation and many patients appear acutely ill. Chest examination often reveals inspiratory crackles and bronchial breath sounds. Dullness to percussion may be observed in lobar consolidation or a parapneumonic pleural effusion is present.[6]

The diagnosis of pneumonia may be made by the isolation of the organism from the sputum or other lung washing samples or by a rise in the specific anti body titer. The results of these methods require several weeks to become positive and the diagnosis must initially be made upon clinical findings.[7]

DIAGNOSIS

Frequently difficult to work out if pulmonary abnormalities are related to the underlying disease or because of the medication. Discontinuance of the offending agent is often followed by spontaneous improvement, whereas failure to appreciate the causal relationship between the drug and the pulmonary disease can lead to irreversible lung injury or death.[8] The diagnosis of dug induced interstitial lung disease (DILD)is usually based on several criteria

(1) A history of drug exposure with correct identification of the drug, its dose, and its frequency.
(2) Clinical, imaging and histopathological patterns which are according to earlier observations with an equivalent drug.
(3) Exclusion of other lung disease.
(4) Improvement following discontinuation of the suspected drugs
(5) Recurrence of symptoms on rechallenge but rechallenge can be hazardous.[9]

Numerous methods for causality assessment of ADR are published and are falling into three categories: expert judgements, algorithms and probabilistic methods. Unfortunately, there is still no method universally accepted for the causality assessment of ADR.[10]

Diagnostic work-up should include a careful examination, laboratory studies, chest radiography and/or high-resolution CT (HRCT) of the chest, pulmonary function testing and-if necessary-invasive procedures such as bronchoscopy. Other non-invasive studies which will be helpful include an echocardiogram, sputum Gram's method and culture, and immunologic studies excluding vasculitis and connective tissue diseases.

TREATMENT

The primary goal of treatment is to suppress the inflammatory response and prevent the deposition of fibrotic tissue.

1. The medication should be withdrawn and the treatment of DILD consists appropriately managing of pulmonary symptoms, after other possibilities are eliminated and DILD is highly suspected. Ideally, symptoms should remit and management includes supportive care. Acute episodes of drug-induced pulmonary disease usually disappear 1-2 days after the drug has been discontinued, but chronic syndromes may take longer to resolve. Because hypoxemia is common in DILD, supplemental oxygen therapy is often prescribed.
2. If the cytotoxic drug-induced disease is severe or appears to progress despite the discontinuation of the drug, an empirical course of glucocorticoids is preferable.
3. If a patient is rechallenged with the drug, symptoms may or may not recur. This is a decision that has to be carefully weighed depending on the severity of the drug-related pulmonary toxicity and the morbidity associated with not treating the underlying disease. If alternative agents are available, they should be used.
4. Because many patients with DILD are treated with immunosuppressive medications and are at some modest increased risk for the development of infections, patients with DILD should receive a pneumococcal vaccine and a yearly influenza virus vaccine.[9]

CASE STUDY

A male patient of age 48years was hospitalized and his chief complaints were shortness of breath grade 4 for 1 day, cough on and off since 1year. He is a known case of multiple myeloma since 5years and on radiotherapy and chemotherapy with bortezomib and thalidomide since 5years, history of similar complaints in the past 1 year and history of blood transfusion 6months back, known case of bronchial asthma since childhood and on inhaler occasionally. The patient was conscious and well oriented to time and place on physical appearance he was weak and his vitals were as follows BP – 110/70 mm Hg, PR – 140/min, CVS – S1S2 (+), RS – BAE (+), B/L Wheeze (+), diffused crept (+). The laboratory investigations shows that the patient had decreased serum chloride levels (87mmol/L), decreased hemoglobin levels (8.7g/dL), decreased hematocrit (27.1%), decreased RBC (3.1 10^6/ul), increased neutrophils (87%), decreased lymphocytes(10%), increased RDW-CV (18%), elevated ESR (100mm 1st hour), x-ray shows pulmonary infiltrates.

So, based on the subjective and objective evidence, the patient was provisionally diagnosed as having acute exacerbation of bronchial asthma with multiple myeloma.

The patient was treated with hydrocortisone (to treat pneumonitis), azithromycin (prophylactic antibiotic) continuous BPAP ventilation, acebrophylline, salbutamol, budesonide, n-acetyl cysteine (for shortness of breath) chlorpheniramine and dextromethorphan (for cough), anti-emetics and anti-ulcer agents. Patient condition was improved after taking hydrocortisone and cancer regimen is discontinued by taking this as the evidence the patient was finally diagnosed as interstitial pneumonia (due to chronic exposure to bortezomib and thalidomide) with multiple myeloma.

DISCUSSION

Thalidomide was developed as an anti-emetic drug in 1950s and found to induce congenital anomalies, so its use is banned. Since 1998, based on the fact that this drug exerts anti-angiogenic and immunomodulatory effects, its use as a standard therapeutic agent for multiple myeloma has increased.[11]

Although the precise mechanism of action of thalidomide is still uncertain, together with its antiangiogenic activity, it appears to have immunomodulatory and anti-cytokine effect and alter the production and activity of cytokines. Since it is postulated that bortezomib affects not only nuclear factor (NF)-kB activity but also various signaling pathways, its metabolites might cause cellular reactions associated with pulmonary injuries in some patient.[12]

In vitro studies with human liver microsomes indicate that bortezomib is primarily oxidatively metabolized through the cytochrome P450 family of enzymes. Although the biotransformation occurs predominantly in

the liver, the lung may be a site of active drug metabolism as well, for the lung has cytochrome P450 enzymes levels estimated at 10 to 15 percent of that of the liver, including the lung-specific cytochrome P450 enzymes. When bortezomib and thalidomide are used together, the adverse effects might synergize and result in severe pulmonary toxicity such as ILD.[2]

CONCLUSION

Physicians should remember this potential complication in patients receiving the novel targeted anticancer agents, bortezomib and thalidomide, who are suffering from dyspnea and new pulmonary infiltrates and fail to enhance despite treatment with broad-spectrum antibiotics.

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