wjpmr, 2019,5(8), 217-219

SJIF Impact Factor: 4.639

WORLD JOURNAL OF PHARMACEUTICAL AND MEDICAL RESEARCH

www.wjpmr.com

Research Article

ISSN 2455-3301

WJPMR

A PROSPECTIVE STUDY OF EARLIER PREDICTION OF BLEOMYCIN INDUCED LUNG TOXICITY IN HODGKIN'S LYMPHOMA & GERMCELL TUMOURS

***Dr. R. Rajakumari MD and Prof. Dr. R. Balajinathan MD**

Department of General Medicine, Madurai Medical College, Madurai India.

***Corresponding Author: Dr. R. Rajakumari MD**

Department of General Medicine, Madurai Medical College, Madurai India.

Article Received on 18/06/2019 **Article Revised on 08/07/2019** **Article Accepted on 29/07/2019**

ABSTRACT

Bleomycin is one of the important chemotherapy commonly given for the treatment of Hodgkin lymphoma and germ-cell tumours, the most highly curable cancers. But bleomycin can cause severe lifethreatening lung injury, which ranges from hypersensitivity pneumonitis and bronchiolitis obliterans organizing pneumonia (BOOP) to acute interstitial pneumonia and progressive pulmonary fibrosis. Pulmonary toxicity is a known side effect of chemotherapy, but a 10% death rate of bleomycin is judged unacceptable for patients with curable cancers. Toxic effects of bleomycin are generally due to formation of free radicals and organ specificity is driven by the bleomycin catalysing hydrolase, which is absent in lung and skin tissue, rendering these organs vulnerable to toxicity. Hence early diagnosis, treatment, and prevention of limiting toxicities such as bleomycin-induced lung injury, is very important. This study aims at of earlier prediction of bleomycin induced lung toxicity in hodgkin's lymphoma & germcell tumours.

KEYWORDS: *bleomycin, Hodgkin's lymphoma, pulmonary fibrosis, germ cell tumour.*

I. INTRODUCTION

Bleomycin is one of the first described chemotherapeutic agents which is used for cancer therapy for many years. Despite the development of newer drugs in oncology, bleomycin remains an important component of chemotherapy for curable diseases such as Hodgkin's lymphoma and germ cell tumours. These cancers commonly affect young individuals who may survive for long periods. In this regard early diagnosis and treatment and prevention of toxicities such as bleomycin induced lung injury is crucial. This article addresses this important side effect predicting it earlier.

II. Aims and objectives

1. To identify the patients developing lung toxicity for Bleomycin in hodgkin's lymphoma and germcell tumour**.**
2. To evaluate the association between PFT and HRCT findings.

III. METHODOLOGY

Hodgkin's lymphoma and germ cell tumour patients of varying age and sex were selected. Their consent was taken. The history was elicited. Age, height weight were recorded. Thorough clinical examination were carried out. The performance of baseline PFT was carried out. In all the patients relevant information will be collected in a predesigned proforma.

The patients are selected based on clinical examinations, histopathological examination and immunohistochemistry. The patients are followed over a period of 6 months with pulmonary function test and HRCT at regular intervals.

LABORATORY INVESTIGATIONS

a) Complete blood count
b) Liver function test
c) Renal function test
d) Sputum AFB
e) Sputum Culture and sensitivity
f) HPE
g) IHC
h) Chest X ray
i) PFT
j) HRCT

DESIGN OF STUDY

Prospective and observational study.

PERIOD OF STUDY

6 months (March 2018 to August 2018).

IV. DISCUSSION

The mechanism of bleomycin-induced lung injury is not entirely clear but likely involves oxidative damage, relative deficiency of the deactivating enzyme bleomycin

hydrolase, genetic susceptibility, and elaboration of inflammatory cytokines.

Bleomycin induces the generation of reactive oxygen radicals by forming a complex with. Consistent with a direct pathologic role for this mechanism, iron chelators ameliorate the pulmonary toxicity of bleomycin in animal models. Reactive oxygen species can produce direct toxicity through participation in redox reactions and subsequent fatty acid oxidation, which leads to membrane instability. Oxidants can cause inflammatory reactions within the lung. For example, the oxidation of arachidonic acid is the initial step in the metabolic cascade that produces active mediators including prostaglandins and leukotrienes. Cytokines such as interleukin-1, macrophage inflammatory protein-1, platelet-derived growth factor (PDGF), and transforming growth factor (TGF)- are released from alveolar macrophages in animal models of bleomycin toxicity, resulting in fibrosis. Damage and activation of alveolar epithelial cells may result in the release of cytokines and growth factors that stimulate proliferation of myofibroblasts and secretion of a pathologic extracellular matrix, leading to fibrosis.

Specifically, TGF-, PDGF receptor- (PDGFR-), and tumor necrosis factor- (TNF-) are believed to stimulate the transformation, proliferation, and accumulation of fibroblasts, which leads to the deposition of extracellular matrix. The progressive accumulation of this collagen matrix causes distortion and destruction of alveolar structures and, eventually, loss of lung function. In animal models, it has been demonstrated that PDGFR- expression is increased in BIP. PDGFR- has also been shown to be increased in epithelial cells and alveolar macrophages in the lungs of patients with idiopathic pulmonary fibrosis. Recent evidence obtained using a bleomycin-induced lung fibrosis model indicates that some fibroblasts in fibrosis may be formed from bone marrow progenitors, as well as from epithelial cells through epithelial-mesenchymal transition.

Cytotoxic drugs may also affect the local immune system. Because the lung is exposed to numerous substances that can activate its immune system, there appears to be pulmonary immune tolerance, which avoids overreactions. This tolerance may, in part, be the result of an effector and suppressor cell balance. Cytotoxic drugs can alter the normal balance, leading to tissue damage.

Other homeostatic systems within the lung can also be affected, such as the balance between collagen formation and collagenolysis. Bleomycin may upregulate collagen synthesis by modulating fibroblast proliferation through a TGF- response. Excessive collagen deposition may result in severe, irreversible pulmonary fibrosis. Bleomycin also has profound effects on the fibrinolytic system, altering the balance between fibrin deposition and fibrinolysis on the alveolar surface, thereby leading to fibrin deposition.

The alveolar macrophage is thought to play a central role in the development of bleomycin-induced lung injury due to its ability to induce the release of a number of effector molecules (e.g., cytokines, lipid metabolites, and oxygen radicals). The mechanism by which alveolar macrophages are activated is unknown. Bleomycin receptors have been identified on the surfaces of rat alveolar macrophages, suggesting that macrophage activation may occur via a second messenger

Bleomycin-containing regimens remain the standard of care for HL and for patients with intermediate and poorrisk GCTs. Those patients need close medical monitoring for early diagnosis of lung toxicity to prevent morbidity and mortality

V. RESULT

Totally 30 patients among which 18 hodgkin's lymphoma and 12 germ cell tumour patients admitted in the Govt Rajaji Hospital were studied for bleomycin induced lung toxicity during march 2018 to August 2018. Age of the subject varied from 18 to 60 years of age. Mean value of age is 42 years
Male were 18 female were 12.
Most of the HL and GCT patients were in the stage 3 disease.

Selected patients were free from previous lung disease as screened by PFT and HRCT.

After completing the course of chemotherapy for HL and GCT patients they were assessed. 12 patients developed symptom among which 9 had dry cough and 3 had dyspnoea.

All patients were subjected to PFT at the end of the treatment. 9 of them developed abnormal PFT in the form of obstruction in 5 patients, restrictive pattern in 3 patients and mixed form in 1 patient.

When HRCT was repeated for these patients they did not show any abnormality.

Since bleomycin toxicity is not only dose dependent these patients have to be further followed up for a minimum of 2 years for earlier identification of bleomycin induced toxicity.

VI. CONCLUSION

Bleomycin-induced lung injury is a major pulmonary toxicity. The mortality of this complication is high, ranging from 10 to 20%, and significantly impacts quality of life and five-year overall survival. The diagnosis of interstitial lung disease and BIP is particularly challenging and often depends on clinical, radiological, and cytological findings. Progress in

understanding the mechanisms behind the therapeutic efficacy and unwanted toxicity of bleomycin, as well as elucidation of its biosynthetic pathway, may lead to the development of agents capable of preventing or treating BIP. Until then, physicians administrating bleomycin should be aware of potential lung toxicity, especially in the presence of risk factors.

REFERENCES

1. S. Sleijfer, "Bleomycin-induced pneumonitis," Chest, 2001; 120(2): 617–624.
2. J. Spence, T. Krings, K. G. TerBrugge, L. B. Da Costa, and R. Agid, "Percutaneous sclerotherapy for facial venous malformations: Subjective clinical and objective MR imaging follow-up results," American Journal of Neuroradiology, 2010; 31(5): 955–960.
3. R. M. Burger, J. Peisach, and S. B. Horwitz, "Activated bleomycin. A transient complex of drug, iron, and oxygen that degrades DNA," The Journal of Biological Chemistry, 1981; 256(22): 11636–11644.
4. J. Chen and J. Stubbe, "Bleomycins: towards better therapeutics," Nature Reviews Cancer, 2005; 5(2): 102–112.
5. E. Chu and V. T. DeVita Jr., Cancer Chemotherapy Drug Manual, Jones and Bartlett, Boston, Mass, USA, 2011.
6. A. A. Ferrando, A. M. Pendás, E. Llano, G. Velasco, R. Lidereau, and C. López-Otín, "Gene characterization, promoter analysis, and chromosomal localization of human bleomycin hydrolase," The Journal of Biological Chemistry, 1997; 272(52): 33298–33304.
7. P. J. Santrach, F. B. Askin, R. J. Wells, R. G. Azizkhan, and D. F. Merten, "Nodular form of bleomycin-related pulmonary injury in patients with osteogenic sarcoma," Cancer, 1989; 64(4): 806–811.
8. K. Jules-Elysee and D. A. White, "Bleomycin-induced pulmonary toxicity," Clinics in Chest Medicine, 1990; 11(1): 1–20.
9. A. B. Simpson, J. Paul, J. Graham, and S. B. Kaye, "Fatal bleomycin pulmonary toxicity in the west of Scotland 1991-95: a review of patients with germ cell tumours," British Journal of Cancer, vol. 78, no. 8, pp. 1061–1066, 1998.
   G. Kessell, S. Panchatsharam, E. Kothmann et al., "General anaesthesia for intralesional bleomycin therapy of vascular malformations: initial 3 yr experience," British Journal of Anaesthesia, 2009; 102(3): 431–432.
10. I. Uzel, M. Ozguroglu, B. Uzel et al., "Delayed onset bleomycin-induced pneumonitis," Urology, 2005; 66(1): 195e.23–195e.25.
11. G. Bollée, C. Sarfati, G. Thiéry et al., "Clinical picture of Pneumocystis jiroveci pneumonia in cancer patients," Chest, 2007; 132(4): 1305–1310.
12. P. W. Van Barneveld, D. T. Sleijfer, T. W. van der Mark et al., "Natural course of bleomycin-induced pneumonitis. A follow-up study," American Review of Respiratory Disease, 1987; 135(1): 48–51.
13. E. H. Herman, B. B. Hasinoff, J. Zhang et al., "Morphologic and morphometric evaluation of the effect of ICRF-187 on bleomycin-induced pulmonary toxicity," Toxicology, 1995; 98(1–3): 163–175.