International Journal of Multiphysics
Volume 18, No. 3, 2024
ISSN: 1750-9548

Effect of Bleomycin on The Lung

Sally Ahmed Selim, Samar Ramzy Mohamed Eid, Sanaa Abdelsalam Mohamed Faisal, Karima Fawzy Abdelfadeel

Department of Medical Histology and Cell Biology, Faculty of Medicine, Zagazig University

***Corresponding author:** Sanaa Abdelsalam Mohamed Faisal

Email: dr.sanaaabdelsalamfaisal@gmail.com

Abstract

Bleomycin is a chemotherapeutic agent known for its efficacy against several malignancies. However, its potential to induce pulmonary toxicity poses significant clinical challenges. This review explores the historical background, molecular mechanisms, histological patterns, clinical features, diagnostic tools, risk factors, and recent therapeutic advancements related to bleomycin-induced pulmonary injury.

Keywords: Bleomycin, Pulmonary Fibrosis, Lung Toxicity, Chemotherapy, Interstitial Lung Disease.

Introduction

Bleomycin, a glycopeptide antibiotic isolated from Streptomyces verticillus, has long been employed in oncology for its cytotoxic effects. Introduced in the 1960s, it became a cornerstone in the treatment of Hodgkin's lymphoma, testicular cancer, and other germ cell tumors. However, its use is often limited due to its potentially fatal pulmonary toxicity. Bleomycin-induced pulmonary toxicity (BPT) is a multifactorial process with incidence rates ranging from 10-25%, depending on cumulative dose, patient age, renal function, and concomitant oxygen therapy (1). This article presents a comprehensive review of the pathophysiology, clinical spectrum, diagnosis, and management of BPT while discussing recent research trends and therapeutic advances.

Bleomycin induces pulmonary injury through several interconnected mechanisms. It binds to DNA, forming free radicals that cause strand breaks and chromosomal aberrations. In the lungs, this results in direct damage to alveolar epithelial cells, endothelial injury, and a cascade of inflammatory responses. Activation of the transforming growth factor-beta (TGF-β) pathway is a key driver of fibroblast proliferation and extracellular matrix deposition (2).

The SMAD-dependent transcription factors further propagate fibrosis. Other molecules implicated include IL-6, TNF-alpha, and PDGF. Additionally, the lungs' low concentration of bleomycin hydrolase, an enzyme that deactivates bleomycin, renders them particularly vulnerable (3).

Recent studies have also shown that inhibition of the JAK/STAT signaling pathway and MRTF/SRF transcriptional activity reduces inflammation and fibrotic progression (4,5). These pathways are being investigated as potential therapeutic targets to mitigate BPT.

Histopathological and Radiological Features

Bleomycin-induced changes on histology and imaging evolve with time. Early histopathological changes include alveolar damage, edema, and infiltration of inflammatory cells. This may progress to organizing pneumonia and finally end-stage pulmonary fibrosis, resembling idiopathic pulmonary fibrosis. Characteristic features include fibroblastic foci, thickening of alveolar septa, and deposition of collagen (3).

On imaging, HRCT is the gold standard for evaluation. Ground-glass opacities, reticular patterns, traction bronchiectasis, and honeycombing are typically observed. These findings often begin in the lower lobes and may be asymmetrical. 18-FDG PET/CT imaging has been proposed as a tool for early detection of metabolic changes before structural damage is evident (6). This early detection is critical for timely cessation of bleomycin and initiation of therapy.

Risk Factors and Genetic Susceptibility

Numerous patient and treatment-related factors contribute to the risk of BPT. The most significant is the cumulative dose, with risk sharply increasing above 400 IU. Older patients (>70 years), those with underlying pulmonary disease, and patients receiving concurrent chest radiation are also at elevated risk (7).

Renal dysfunction leads to drug accumulation, thereby increasing toxicity. Furthermore, the use of supplemental oxygen during or after bleomycin therapy—particularly at high concentrations—exacerbates oxidative stress, worsening lung injury. Genetic predispositions also play a role. Polymorphisms in genes such as MUC5B, TOLLIP, and surfactant proteins have been investigated, though results are inconclusive. Genomic and transcriptomic studies may soon help stratify patients based on risk and personalize treatment protocols (8).

Clinical Presentation

Clinical symptoms of BPT typically present within 1–6 months after initiation of therapy. Patients may report dry cough, exertional dyspnea, low-grade fever, and chest discomfort. Physical findings include bibasilar rales and, in severe cases, signs of hypoxemia. In advanced stages, BPT can mimic acute respiratory distress syndrome (ARDS) with severe hypoxia requiring mechanical ventilation. Interestingly, some patients may remain asymptomatic despite significant radiographic abnormalities. This underscores the need for routine pulmonary monitoring in high-risk patients, even in the absence of overt clinical symptoms (3).

Diagnostic Approach

Diagnosis of BPT remains challenging due to its non-specific symptoms and overlap with other pulmonary conditions, especially infections. The initial workup includes imaging (chest X-ray and HRCT), pulmonary function tests (PFTs), and exclusion of infectious etiologies. A significant decline in DLCO (>20%) is often the earliest indicator of bleomycin toxicity and warrants further evaluation (9). Bronchoalveolar lavage (BAL) can help rule out infection and may show lymphocytic predominance in BPT. In selected cases, video-assisted thoracoscopic lung biopsy may be required for definitive diagnosis. Radiologists and pulmonologists must collaborate to interpret findings in the context of clinical and treatment history.

Prevention and Management

Prevention remains the best strategy for BPT. This includes dose limitation, close monitoring of respiratory symptoms, and avoidance of high-concentration oxygen during and after treatment. Regular pulmonary function monitoring (particularly DLCO) is recommended for all patients receiving bleomycin. Once toxicity is suspected or diagnosed, immediate discontinuation of bleomycin is essential. Systemic corticosteroids are the cornerstone of treatment, with doses ranging from 0.5 to 1 mg/kg/day of prednisone or its equivalent. However, evidence supporting their efficacy is limited to case series and anecdotal reports (3).

Newer antifibrotic agents such as pirfenidone and nintedanib, approved for idiopathic pulmonary fibrosis, are under investigation in BPT. Experimental therapies, including imatinib (a tyrosine kinase inhibitor) and baricitinib (a JAK inhibitor), have shown promising preclinical results (1,4,10). Clinical trials are needed to validate their role in routine practice.

Recent Advances and Research

Recent years have witnessed a surge in research on the molecular underpinnings and potential treatments for BPT. Imatinib, targeting PDGF and TGF-β signaling, has demonstrated reversal of fibrosis in animal models and isolated case reports in humans (1). Baricitinib, by inhibiting JAK1/2 pathways, suppressed cytokine signaling and decreased fibrotic markers in murine models (4). Sesamol, a natural antioxidant, reduced oxidative stress, lipid peroxidation, and inflammatory cytokines in rat models exposed to bleomycin (2). Nootkatone, derived from grapefruit, exerted protective effects in lung cancer cell lines via modulating oxidative stress pathways (4).

Furthermore, inhibitors of the myocardin-related transcription factor/serum response factor (MRTF/SRF) axis have been found to limit fibroblast activation and collagen deposition (5). These discoveries offer new avenues for therapeutic intervention and may redefine the management of BPT in the coming decade.

Conclusion

Bleomycin-induced pulmonary toxicity represents a significant clinical challenge with serious implications. Understanding its multifactorial pathogenesis, identifying patients at risk, and applying timely interventions are paramount. While corticosteroids remain the mainstay of therapy, emerging evidence suggests that targeted molecular therapies may soon provide more effective and personalized treatment options. As research progresses, incorporating genomic profiling, early imaging biomarkers, and novel pharmacologic agents may transform the clinical landscape of BPT management. Further large-scale clinical trials and long-term outcome studies are urgently needed to validate these approaches and improve patient survival and quality of life.

References

1. Aykaç N, Tecimer C. Imatinib treatment for bleomycin-induced pulmonary toxicity. Turk Thorac J. 2020;21(6):457-460.
2. Kaushik S, Bhargava P, Sharma J, et al. Sesamol attenuates bleomycin-induced pulmonary toxicity and fibrosis in experimental animals. J Biochem Mol Toxicol. 2023;37(11):e23472.
3. Zhao, Y., Yan, Z., Liu, Y., Zhang, Y., Shi, J., Li, J., & Ji, F. Effectivity of mesenchymal stem cells for bleomycin-induced pulmonary fibrosis: a systematic review and implication for clinical application. Stem cell research & therapy, 2021, 12(1), 470.
4. Gu S, Liang J, Zhang J, et al. Baricitinib attenuates bleomycin-induced pulmonary fibrosis in mice by inhibiting TGF-β1 signaling pathway. Molecules. 2023;28(5):2195.
5. Santos-Ribeiro D, Lecocq M, de Beukelaer M, et al. Bleomycin-induced lung injury: Revisiting an old tool. Pulm Circ. 2023;13(1):e12177.
6. Shaikh H, Omer Z, Jandarov RA, et al. FDG PET/CT as a tool for early detection of bleomycin-induced pulmonary toxicity. Lymphatics. 2023;1(1):45-54.
7. Zhao, Y., Yan, Z., Liu, Y., Zhang, Y., Shi, J., Li, J., & Ji, F. Effectivity of mesenchymal stem cells for bleomycin-induced pulmonary fibrosis: a systematic review and implication for clinical application. Stem cell research & therapy, 2021, 12(1), 470.
8. Pan, L., Cheng, Y., Yang, W., Wu, X., Zhu, H., Hu, M., ... & Zhang, M. Nintedanib ameliorates bleomycin-induced pulmonary fibrosis, inflammation, apoptosis, and oxidative stress by modulating PI3K/Akt/mTOR pathway in mice. Inflammation, 2023, 46(4), 1531-1542.
9. Gundogan, B. D., Taskinlar, S., Arikoglu, T., Balci, Y., & Citak, E. C. (2022). Bleomycin-induced Pneumonitis in a child treated with Nintedanib: report of the first case in a childhood. Journal of Pediatric Hematology/Oncology, 44(2), e500-e502.
10. Sani, S. M. S., Sahranavard, M., Yazdanabad, M. J., Shamsi, M. S., Elyasi, S., Mohammadpour, A. H., ... & Sahebkar, A. (2022). The effect of concomitant use of Colony-Stimulating factors on bleomycin pulmonary toxicity–A systematic review and meta-analysis. International Immunopharmacology, 112, 109227.