REVIEW ARTICLE

Pharmacological Approach for Prevention of Bleomycin-Induced Lung Injury

Mohammad Ayoubifar[1], Farshad Abedi[2], Mohammad Moeini Nodeh[3], Omid Arasteh[2*]

[1]School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

[2]Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran.

[3]Division of Hematology and Oncology, Department of Internal Medicine, School of Medicine, Mashhad University of Medical Sciences Mashhad, Iran.

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Abstract

Bleomycin is a chemotherapeutic medication commonly use in the treatment of Hodgkin's disease and germ cell tumors. Pulmonary fibrosis is major and dose limiting adverse effect of the drug. There is not currently any equal alternative approach or a medical agent for prevention of its pulmonary injury. We searched scientific databases in order to find investigational pharmacologic medicines in prevention of bleomycin-induced lung toxicity (BILI). Results revealed that some anti-inflammatory and antioxidant preparations such as statins, N-acetylcysteine (NAC), supplements (vitamin D3, L-arginine, selenium), and renin-angiotensin-aldosterone system (RASS) inhibitors might be effective in preclinical models of pulmonary toxicity mediated by bleomycin. However, we still need more in vivo studies and large human randomized clinical trials to confirm their benefits.

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Keywords: Bleomycin; Lung Injury; Antioxidant; Anti-inflammatory

Introduction

Bleomycin is an antineoplastic agent which first isolated from the fungus Streptomyces verticillus and was discovered by Umezewa in 1966. It is used mainly in the first line treatment protocols of Hodgkin's disease and germ-cell malignancies. Additionally, bleomycin is used to treat a variety of tumors, including Kaposi's sarcoma, cervical cancer, and head and neck squamous cell carcinomas (1). The most frequent adverse effects of bleomycin include skin reaction, mucositis, fever, and more importantly pulmonary toxicity (2).

The main drawback of bleomycin therapy is typically pulmonary toxicity and fibrosis, which has been reported in up to 10% of patients taking the medication and can be fatal. Bleomycin causes lung damage through two stages. Inflammation in the lungs occurs during the first stage, which is characterized by the invasion of inflammatory cells like macrophages, neutrophils, and lymphocytes. The second phase, which is marked by collagen deposition and involves fibrosis, follows this. Lung architecture deformation and excessive matrix deposition brought by pulmonary fibrosis and result in respiratory failure and mortality (3). The exact mechanism of bleomycin-induced lung damage is unknown, although it probably involves oxidative damage, as a result of relative lack of bleomycin hydrolase in the lungs. Bleomycin hydrolase is an enzyme principally in charge of metabolizing bleomycin into harmless compounds (4, 5). Older age, renal insufficiency, higher cumulative doses of bleomycin (>400 units), thoracic irradiation, exposure to high partial pressure of oxygen, cigarette smoking, and concurrent administration of granulocyte colony stimulating factors (GCSF) and cisplatin at high doses are major risk factors for development of bleomycin-induced lung injury (BILI) (6, 7).

The mainstay of treatment for BILI is to permanently discontinuing the drug. Systemic glucocorticoids may also use in some symptomatic acute or subacute cases. Bleomycin cannot be reintroduced in these patients and there is no equally effective alternative antineoplastic agent for the patient's disease (3, 8). So, preventing pulmonary toxicity seems to be the best strategy for management. Lowering the total cumulative dose of bleomycin is one of the most effective approaches to stop BILI. However, there is always concern about becoming less effective when we reduce the standard dose of a chemotherapy drug (9).

Recent advances have been better characterized the pathophysiology and diagnosis of BILI but there is not effective preventive therapy, yet. Therefore, finding new medications to prevent and treat BILI is crucial. In this

Corresponding Author: Dr Omid Arasteh
Address: Department of Clinical Pharmacy, School of Pharmacy, Mashhad University of Medical Sciences, Mashhad, Iran. Tel: +989151804989.
Email: ArastehO@mums.ac.ir

article, we will review some of the proposed treatments that have been carried out on human and animal samples in order to prevent BILI.

Methods

This review was conducted by using the PubMed, Google Scholar and Web of Science databases to gain relevant studies about BILI and the effects of pharmacological agents. Following keywords were included first: "bleomycin" AND "lung injury" OR "pulmonary toxicity" AND "medicine" OR "drug" AND "prevention" OR "treatment". General related keywords were first chosen so that the search results become wide enough not to miss out on any related title. Then the most relevant articles were retrieved among them. Afterwards, a second search was specifically conducted with each yielded drug name(s). Studies were identified from 2000 up to October 2022. No limitation was exerted in the advanced searching.

Results

After screening of 302 papers, we found 17 relevant articles regarding possible benefits of statins, renin-angiotensin-aldosterone system (RASS) inhibitors, N-acetylcysteine (NAC), supplements, heparin, thalidomide, felodipine, amitriptyline, and gemfibrozil on BILI. Among 17 relevant papers, we found one retrospective cohort study and 16 animal studies on rat, mouse or rabbit. Herein, details of each study were described according to the medicine that is used. Results also have been summarized in Table 1.

Figure1. Preventive and risk factors of bleomycin-induced lung injury.

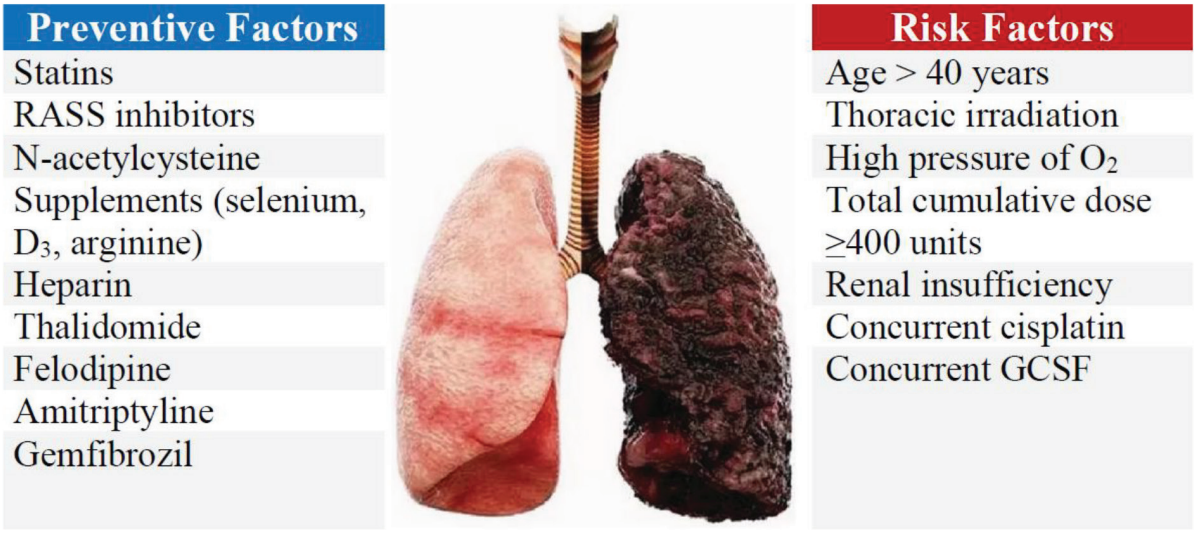

Table 1. Characteristics of the included studies.

First Author, Year	Type of study	Bleomycin administration	Intervention(s)	Result(s)	Proposed mechanism(s)
A Serrano-Mollar, 2003	Animal study (Rat model)	2.5 Units/kg intratracheal at Day 8	N-acetylcysteine intraperitoneal 300 mg/kg at Days 1 to 23	Less augmented lung wet weight, and lower levels of proteins, lactate dehydrogenase, neutrophil and macrophage counts in bronchoalveolar lavage fluid and lung myeloperoxidase activity with a betterment of histological score at Day 11 Less collagen deposition at Day 23	Antioxidant effects by preservation of GSH/GSSG ratio and reduction of lipid hydroperoxides, nitric oxide and NF-kB Anti-inflammatory effects by reduction of TNF-α, IL-B, IL-6 and macrophage inflammatory protein-2
Andreas Günther, 2003	Animal study (Rabbit model)	1.8 Units/kg nebulization at Day 0	Heparin nebulization 3,500 Units at Days 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, and 24	Far-reaching normalization of compliance, suppression of soluble collagen and hydroxyproline accumulation, and virtual abrogation of the CT scan and histologic features of lung fibrosis	Anticoagulation prevents lung fibrosis
Baykal Tulek, 2012	Animal study (Rat model)	2.5 Units/kg intratracheal at Day 2	Simvastatin intraperitoneal 5 mg/kg at Days 1 to 15	Partial improvement in profibrotic cytokine levels No effect on lung tissue hydroxyproline content and histopathological	Reduction of IL-13 and TGF-β1 levels

Table 1. Continued

First Author, Year	Type of study	Bleomycin administration	Intervention(s)	Result(s)	Proposed mechanism(s)
Bo Zhu, 2013	Animal study (Rat model)	1 mg/kg intratracheal at Day 0	Atorvastatin orally 10 mg/kg at Days 1 to 28	Ameliorated the bleomycin mediated histological alterations and blocked collagen deposition with parallel reduction in the hydroxyproline level. Atorvastatin also reduced malondialdehyde (MDA) level and lung indices	Suppression of iNOS expression and the connective tissue growth factor (CTGF (CCN2)) and phosphorylation extracellular regulated protein kinases (p-ERK) signaling Pathway
C.P. Liu, 2014	Animal study (Mouse model)	4 Units/kg intratracheal at Day 0	Simvastatin intraperitoneal 5 mg/kg at Days 1 to 7 or Days 1 to 28	Attenuated histologic collagen disposition and reduced BALF inflammatory cells Reduced inflammation and delayed fibrosis	Restore of eNOS and inhibition of iNOS/ROCKII/ MMP-2/MMP-9
Chiharu Tabata, 2007	Animal study (Mouse model)	2 mg/kg intraperitoneal at Days 1, 8, and 15	Thalidomide intraperitoneal 4 mg five times weekly for four weeks	Ameliorated fibrosis, reduced lung angiogenesis	Decrease of the expressions of IL-6, TGF-β1, VEGF, Ang-1 Ang-2, and COL1A1 mRNA
J Cortijo, 2001	Animal study (Rat model)	2.5 Units/kg intratracheal at Day 8	N-acetylcysteine orally 3 mmol/kg at Days 1 to 21	Partially decreased the augmented collagen deposition by reduction of hydroxyproline content Lessen collagen deposition and inflammatory cells	Antioxidant effects by increasing total glutathione and taurine levels in bronchoalveolar lavage fluid
Jianjun Chang, 2021	Animal study (Mouse model)	1.5 Units/kg intratracheal at Day 0	Paricalcitol intraperitoneal 150 ng/kg at Days 2, 4, 6, 8, 10, 12, 14, 16, 18, 20, 22, 24, 26, and 28	Prevented weight loss and alleviated lung fibrosis, suppressed the induction of fibrotic inducer TGF-β and extracellular matrix proteins α-SMA, collagen type I and fibronectin in the lung	Suppression of the local renin–angiotensin system (RAS) in the lung
Junichi Tanaka, 2013	Animal study (Mouse model)	2 mg/kg intratracheal at Day 6	Irbesartan orally 20 mg/kg at Days 1, 2, 3, 4, and 5	Reduced the fluid content and hydroxyproline level in the lung and improved the pathological findings as indicated by the Ashcroft score. Total cell counts, the numbers of macrophages, neutrophils, and lymphocytes, and the levels of TGF-β1 and monocyte chemotactic protein 1 in the bronchoalveolar lavage fluid were decreased at Day 20	Angiotensin receptor blockers (ARBs) and peroxisome proliferator-activated receptor (PPAR) γ ligands have anti-inflammatory and anti-fibrotic effects
Kelly C Teixeira, 2007	Animal study (Mouse model)	2.5 Units/kg intratracheal at Day 0	N-acetylcysteine intraperitoneal 20 mg/kg plus Deferoxamine intraperitoneal 30 mg/kg at Days 1 to 60	Inhibited lung lesion, decreased total cell counts, neutrophils, LDH, malondialdehyde equivalents and carbonyl contents	Reduction of inflammatory indicators and oxidative stress
Ken-Ichiro Tanaka, 2017	Animal study (Mouse model)	1 or 2 mg/kg intratracheal at Day 0	Felodipine intratracheal 3.3 mg/kg at Days 10, 11, and 12	Prevented bleomycin-induced pulmonary fibrosis, alteration of lung mechanics and respiratory dysfunction, suppressed the activated fibroblasts in the lung	Inhibition of TGF-β1 and fibroblasts-induced collagen production

Table 1. Continued

First Author, Year	Type of study	Bleomycin administration	Intervention(s)	Result(s)	Proposed mechanism(s)
Lu Gao, 2019	Animal study (Mouse model)	5 mg/kg intratracheal at Day 0	L-Arginine orally 1800 mg/kg at Days 1 to 28	Dynamically reversed the weight loss, decreased lung index and hydroxyproline, and improved lung histopathological damages	Corrective action on immune imbalance, arginine metabolism disorder
Mai A Zaafan, 2019	Animal study (Rat model)	5 mg/kg intratracheal at Day 0	Amitriptyline orally 10 mg/kg at Days 1 to 21	Potent antifibrotic effect that was reflected upon the histopathological examination and suppress all the fibrotic parameters	Anti-inflammatory and antifibrotic effects by inhibition of NF-κβ, Nrf2, iNOS, and p53 and other oxidative stress and inflammatory mediators in lung tissue
Rana Shahabi, 2018	Animal study (Rat model)	4 mg/kg intratracheal at Day 0	Selenium nanoparticle intraperitoneal 0.5 mg/kg at Days 1 to 5	Improved the degree of alveolitis and inflammation and lung structure damage	Decrease of TGF-β1 in the lung and TNF-α levels in the serum and lung homogenates
Ryujiro Hara 2021	Retrospective cohort study	190 patients treated with a bleomycin-containing regimen for Hodgkin lymphoma or germ cell tumors	RAAS inhibitor use for hypertension treatment	Might reduce the onset of bleomycin-induced lung injury	RAAS inhibition
Yasna Mohammadi 2017	Animal study (Rat model)	5 Units/kg intratracheal at Day 4	Gemfibrozil orally 5, 50, and 100 mg/kg at Days 1 to 24	Beneficial effects on lung inflammation and fibrosis in a dose-dependent manner	Antioxidative and anti-inflammatory effects
Zeki Yildirim 2005	Animal study (Rat model)	2.5 Units/kg intratracheal at Day 2	N-acetylcysteine orally 3 mmol/kg at Days 1 to 16	Reduced hydroxyproline content, reduced depletion of glutathione peroxidase, and prevented increases in myeloperoxidase activities, nitric oxide, and malondialdehyde levels in lung tissue	Antioxidant effects

Statins

Statins act by 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibition and clinically use for the treatment of dyslipidemia and primary or secondary prevention of cardiovascular events (10, 11). Moreover, experimental and clinical evidence has revealed that statins inhibit inflammation and oxidative stress. Positive results in experimental trials have been obtained in numerous respiratory disease models such as asthma, smoking-induced emphysema, pulmonary hypertension, idiopathic pulmonary fibrosis, acute lung injury and lung transplantation (12, 13). These findings suggested that statins could be beneficial in the treatment of pulmonary fibrosis.

In a rat model of BILI, simvastatin administration reduced intrelukin-13 (IL-13) and transforming growth factor-β1 (TGF-β1) levels and partially improved profibrotic cytokine levels. But no effect on lung tissue hydroxyproline content and histopathological were found (14). In another rat model study by Bo Zhu, et al (2013), atorvastatin ameliorated the bleomycin mediated histological alterations and blocked collagen deposition with parallel reduction in the hydroxyproline level. Atorvastatin also reduced malondialdehyde level and lung indices (15). Also, in a mouse model, simvastatin delayed fibrosis by attenuation of histologic collagen disposition and reduced bronchoalveolar lavage fluid (BALF) inflammatory cells (16).

Renin-angiotensin-aldosterone System Inhibitors

The renin-angiotensin-aldosterone system (RASS) is primarily related with increasing blood pressure by modulating blood volume through water reabsorption and vascular tone, sodium reabsorption, and potassium secretion (17, 18). RAAS is also associated with apoptosis, inflammation, and fibrosis (19). RAAS inhibitors including angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers

(ARBs) are demonstrated to suppress fibrosis of the lung in several studies (20).

Interestingly, in a mouse model of BILI by Junichi Tanaka, et al (2013), irbesartan as an ARB reduced the fluid content and hydroxyproline level in the lung and improved the pathological findings of the lung. Total cell counts, the numbers of macrophages, neutrophils, and lymphocytes, and the levels of TGF-β1 and monocyte chemotactic protein-1 in the bronchoalveolar lavage fluid were also decreased (21). Moreover, in a retrospective cohort of 190 patients who were treated with a bleomycin-containing regimen for Hodgkin lymphoma or germ cell tumors, the effects of RASS inhibitor users on the lung injury incidence were investigated (22). Among 31 patients with hypertension, lung injury developed in 12.5% of patients who were administered RAAS inhibitors compared with 53.3% in those who were not. It is concluded that RASS inhibitors might reduce the onset of BILI.

N-acetylcysteine

N-acetylcysteine (NAC) is a sulfhydryl containing medication with potent antioxidant and anti-inflammatory properties. It is generally used as an antidote of acetaminophen overdose and to loosen thick mucus in chronic bronchopulmonary disorders such as bronchitis and pneumonia (23).

In the first study, NAC demonstrated to partially decrease the augmented collagen deposition and lessen collagen deposition and inflammatory cells in lung of rats exposed to bleomycin. It is proposed that antioxidant effects of NAC by increasing total glutathione and taurine levels in bronchoalveolar lavage fluid is responsible of these effects (24). NAC also attenuated lung injury in rats who received bleomycin via antioxidant and anti-inflammatory effects (25). In another study, NAC revealed to act antioxidant effects by decreasing hydroxyproline content, inhibiting depletion of glutathione peroxidase, and preventing increases in myeloperoxidase activities, nitric oxide, and malondialdehyde levels in lung tissue of rats exposed to bleomycin (26). Furthermore, in a mouse model of BILI, combination of NAC and deferoxamine inhibited lung lesion by reduction of inflammatory indicators and oxidative stress (27).

3.4. Supplements

An essential mineral called selenium is crucial for preventing cancer and neurodegenerative illnesses (28). A lack of selenium has also been linked to a higher risk of chronic inflammatory disorders, including cardiovascular disease and inflammatory bowel disease (IBD). Selenium has been proven in numerous researches to have anti-inflammatory properties. Due to a restricted range between effective and hazardous levels, selenium's bioavailability and toxicity are its limiting variables. Elemental selenium nanoparticles (SeNPs) have drawn a lot of attention due to their novel properties, such as their high surface area, high surface activity, high absorption capacity, high catalytic potential, and lower toxicity (29). SeNPs have been shown in numerous studies to have anti-inflammatory properties both in vivo and in vitro (30).

Protective and anti-inflammatory effect of SeNPs against BILI in male rats was investigated by Shahabi, et al., (2019). In early and late stages of the disease, male rats were used in this study to assess the protective impact of SeNPs against pulmonary injury caused by bleomycin. In both the early phase and late phase, the rats received intraperitoneal injections of SeNPs for five days in a row (a week after injection of bleomycin). The findings demonstrated that early injection of SeNPs reduced lung structural damage, alveolitis, and inflammation to a greater extent. Additionally, compared to the group that received bleomycin, lead to significantly lower levels of serum and lung homogenates, tumor necrosis factor-α (TNF-α), and TGF-β1 density. However, the SeNP therapy did not have any ameliorative benefits during the late period. As a result, the data imply that SeNP protects rats from BILI during the early stages of the illness. This could imply that SeNPs could be a brand-new therapeutic agent for treating this disease in its early stages (31).

Paricalcitol is an analog of 1, 25-dihydroxyergocalciferol, the active form of vitamin D_2. It is generally used for the prevention and treatment of secondary hyperparathyroidism in patients with chronic kidney disease (32, 33). In a mouse model of BILI, paricalcitol administration prevented weight loss and alleviated lung fibrosis, suppressed the induction of fibrotic inducer TGF-β and extracellular matrix proteins α-SMA, collagen type I and fibronectin in the lung. It is proposed that suppression of the local renin–angiotensin system (RAS) in the lung by paricalcitol is responsible for these effects (34).

L-arginine is an essential amino acid that contributes the body build protein. It is found in most protein-rich foods, including fish, red meat, poultry, soy, whole grains, beans and dairy products (35, 36). Furthermore, there are supplement preparations in market and claims to be effective in lowering blood pressure and sugar, reducing the symptoms of angina and peripheral arterial disease, treating erectile dysfunction, and etc. (37, 38). L-arginine also demonstrated promising effects in prevention of lung injury in a mouse model by Gao et al., (2019). After induction of lung injury via bleomycin, treating with L-arginine dynamically reversed the weight loss, decreased lung index and hydroxyproline, and improved lung histopathological damages. Corrective actions on immune system imbalance and correction of arginine metabolism disorders are probably underlying mechanisms of L-arginine lung benefits (39).

Miscellaneous drugs

Heparin is an anticoagulant agent which acts through inhibition of intrinsic pathway of coagulation cascade via binding and activation of antithrombin (40). In a rabbit model of BILI, heparin nebulization resulted in far-reaching normalization of compliance, suppression of soluble collagen and hydroxyproline accumulation,

and virtual abrogation of the computed topography scan and histologic features of lung fibrosis. It is consequently concluded that anticoagulation might prevent lung fibrosis (41).

Thalidomide is an antineoplastic medication and angiogenesis inhibitor used to treat some cancers such as multiple myeloma, graft-versus-host disease, and a number of skin conditions including complications of erythema nodosum leprosum (42, 43). Treatment with thalidomide in a mouse model of BILI ameliorated fibrosis and reduced lung angiogenesis. Molecular examinations revealed reduction in the expressions of IL-6, TGF-β1, vascular endothelial growth factors (VEGFs), Angiotensinogen-1 and 2, and collagen type Iα1 (COL1A1) mRNA in lungs of treated mice (44).

Felodipine is a dihydropyridine calcium channel blocker which is indicated in treatment of hypertension and chronic stable angina (45, 46). In a mouse model, felodipine prevented bleomycin-induced respiratory dysfunction and alteration of lung mechanics. It also suppressed the activated fibroblasts pulmonary fibrosis in the mice lung. Inhibition of TGF-β1 and fibroblasts-induced collagen production proposed as protective mechanism of felodipine against bleomycin lung injury (47).

Amitriptyline effects in prevention and treatment of BILI is also investigated by Zaafan et al., 2019. Amitriptyline belongs to the group of tricyclic antidepressants with broad indications in depression, migraine prevention, irritable bowel syndrome (IBS), neuropathic pain, and etc. (48). Administration of amitriptyline in a rat model of BILI exhibited anti-inflammatory and anti-fibrotic effects. It is reflected upon the histopathological examination of rat lung tissues by inhibition of nuclear factor-κB (NF-κB), nuclear factor erythroid 2–related factor 2 (Nrf2), inducible nitric oxide synthase (iNOS), and p53 and other inflammatory and oxidative stress mediators (49).

Another medication which is repositioned in prevention of bleomycin pulmonary injury is gemfibrozil. It is a fibric acid and lipid lowering agent which is indicated in hypertriglyceridemia and hyperchylomicronemia (50). Gemfibrozil demonstrated that in a dose-dependent manner has beneficial effects on rat lung inflammation and fibrosis (51).

Conclusion

To our knowledge, this is the first publication reporting available pharmacological agents in the prevention of BILI. As seen in the above review, some anti-inflammatory and antioxidant preparations such as statins, N-acetylcysteine, supplements, and renin-angiotensin-aldosterone system (RASS) inhibitors have been studied in order to prevent lung damage caused by bleomycin. Most of the studies are preclinical and only one retrospective cohort study has investigated the effects of RAAS inhibitors on BILI. Statins, NAC and RAAS inhibitors have been mostly studied in this field, which implies their potentials for future human clinical studies. Beneficial effects have been proved to be mediated through inhibition of inflammation and oxidant species. However, most of these drugs were studied on animal models. Considering the importance of preventing the lung toxicity, more in vivo studies and large human randomized clinical trials are still needed to confirm their application in this field.

Conflict of Interests

There is no conflict of interests.

References

1. Sikic BI, Rozencweig M, Carter SK. Bleomycin chemotherapy: Elsevier; 2016.
2. Gerriets V, Kasi A. Bevacizumab. StatPearls [Internet]: StatPearls Publishing; 2022.
3. Reinert T, Baldotto CSdR, Nunes FAP, Scheliga AAdS. Bleomycin-induced lung injury. Journal of Cancer Research. 2013;2013.
4. Schwartz DR, Homanics GE, Hoyt DG, Klein E, Abernethy J, Lazo JS. The neutral cysteine protease bleomycin hydrolase is essential for epidermal integrity and bleomycin resistance. Proc Natl Acad Sci U S A. 1999;96(8):4680-5.
5. Chen J, Chen Y, He Q. Action of bleomycin is affected by bleomycin hydrolase but not by caveolin-1. Int J Oncol. 2012;41(6):2245-52.
6. Camus P. Interstitial lung disease from drugs, biologics, and radiation. Interstitial Lung Disease 5th ed Shelton, CT: People's Medical Publishing House. 2011;637.
7. O'sullivan J, Huddart R, Norman A, Nicholls J, Dearnaley D, Horwich A. Predicting the risk of bleomycin lung toxicity in patients with germ-cell tumours. Ann Oncol. 2003;14(1):91-6.
8. White DA, Stover DE. Severe bleomycin-induced pneumonitis: clinical features and response to corticosteroids. Chest. 1984;86(5):723-8.
9. Einhorn LH, Williams SD, Loehrer PJ, et al. Evaluation of optimal duration of chemotherapy in favorable-prognosis disseminated germ cell tumors: a Southeastern Cancer Study Group protocol. J Clin Oncol. 1989;7(3):387-91.
10. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk: the Task Force for the management of dyslipidaemias of the European Society of Cardiology (ESC) and European Atherosclerosis Society (EAS). Eur Heart J. 2020;41(1):111-88.
11. Rabar S, Harker M, O'Flynn N, Wierzbicki AS. Lipid modification and cardiovascular

risk assessment for the primary and secondary prevention of cardiovascular disease: summary of updated NICE guidance. BMJ. 2014;349.

12. Beltowski J. Statins and modulation of oxidative stress. Toxicol Mech Methods. 2005;15(2):61-92.
13. Sørensen AL, Hasselbalch HC, Nielsen CH, Poulsen HE, Ellervik C. Statin treatment, oxidative stress and inflammation in a Danish population. Redox Biol. 2019;21:101088.
14. Tulek B, Kiyan E, Kiyici A, Toy H, Bariskaner H, Suerdem M. Effects of simvastatin on bleomycin-induced pulmonary fibrosis in female rats. Biol Res. 2012;45(4):345-50.
15. Zhu B, Ma AQ, Yang L, Dang XM. Atorvastatin attenuates bleomycin-induced pulmonary fibrosis via suppressing iNOS expression and the CTGF (CCN2)/ERK signaling pathway. Int J Mol Sci. 2013;14(12):24476-91.
16. Liu C, Kuo M, Wu B, et al. NO-releasing xanthine KMUP-1 bonded by simvastatin attenuates bleomycin-induced lung inflammation and delayed fibrosis. Pulm Pharmacol Ther. 2014;27(1):17-28.
17. Fountain JH, Lappin SL. Physiology, Renin Angiotensin System. 2022 Jun 18. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2022 Jan–.
18. Nehme A, Zouein FA, Deris Zayeri Z, Zibara K. An update on the tissue renin angiotensin system and its role in physiology and pathology. J Cardiovasc Dev Dis. 2019;6(2):14.
19. Pacurari M, Kafoury R, Tchounwou PB, Ndebele K. The renin-angiotensin-aldosterone system in vascular inflammation and remodeling. Int J Inflam. 2014;2014:689360.
20. Gupta D, Kumar A, Mandloi A, Shenoy V. Renin angiotensin aldosterone system in pulmonary fibrosis: Pathogenesis to therapeutic possibilities. Pharmacol Res. 2021;174:105924.
21. Tanaka J, Tajima S, Asakawa K, et al. Preventive effect of irbesartan on bleomycin-induced lung injury in mice. Respir Investig. 2013;51(2):76-83.
22. Hara R, Onizuka M, Shiraiwa S, et al. The role of hypertension and renin-angiotensin-aldosterone system inhibitors in bleomycin-induced lung injury. Clinical Lymphoma Myeloma and Leukemia. 2021;21(4):e321-e7.
23. Šalamon Š, Kramar B, Marolt TP, Poljšak B, Milisav I. Medical and dietary uses of N-acetylcysteine. Antioxidants. 2019;8(5):111.
24. Cortijo J, Cerda-Nicolas M, Serrano A, et al. Attenuation by oral N-acetylcysteine of bleomycin-induced lung injury in rats. Eur Respir J. 2001;17(6):1228-35.
25. Serrano-Mollar A, Closa D, Prats N, et al. In vivo antioxidant treatment protects against bleomycin-induced lung damage in rats. Brit J Pharmacol. 2003;138(6):1037.
26. Yildirim Z, Kotuk M, Iraz M, et al. Attenuation of bleomycin-induced lung fibrosis by oral sulfhydryl containing antioxidants in rats: erdosteine and N-acetylcysteine. Pulm Pharmacol Ther. 2005;18(5):367-73.
27. Teixeira KC, Soares FS, Rocha LG, et al. Attenuation of bleomycin-induced lung injury and oxidative stress by N-acetylcysteine plus deferoxamine. Pulm Pharmacol Ther. 2008;21(2):309-16.
28. Brigelius-Flohé R. Selenium in human health and disease: An overview. Selenium. 2018:3-26.
29. Zhang J, Wang X, Xu T. Elemental selenium at nano size (Nano-Se) as a potential chemopreventive agent with reduced risk of selenium toxicity: comparison with se-methylselenocysteine in mice. Toxicol Sci. 2008;101(1):22-31.
30. Huang Z, Rose AH, Hoffmann PR. The role of selenium in inflammation and immunity: from molecular mechanisms to therapeutic opportunities. Antioxid Redox Signal. 2012;16(7):705-43.
31. Shahabi R, Anissian A, Javadmoosavi SA, Nasirinezhad F. Protective and anti-inflammatory effect of selenium nano-particles against bleomycin-induced pulmonary injury in male rats. Drug Chem Toxicol. 2021;44(1):92-100.
32. Slatopolsky E, Finch J, Ritter C, Takahashi F. Effects of 19-nor-1, 25 (OH) 2D2, a new analogue of calcitriol, on secondary hyperparathyroidism in uremic rats. Am J Kidney Dis. 1998;32(4):S40-S7.
33. Coyne D, Acharya M, Qiu P, et al. Paricalcitol capsule for the treatment of secondary hyperparathyroidism in stages 3 and 4 CKD. Am J Kidney Dis. 2006;47(2):263-76.
34. Chang J, Nie H, Ge X, et al. Vitamin D suppresses bleomycin-induced pulmonary fibrosis by targeting the local renin–angiotensin system in the lung. Sci Rep. 2021;11(1):1-12.
35. Palmer RM, Ashton D, Moncada S. Vascular endothelial cells synthesize nitric oxide from L-arginine. Nature. 1988;333(6174):664-6.
36. Tapiero H, Mathe G, Couvreur P, Tew KI. Arginine. Biomed Pharmacother. 2002;56(9):439-45.
37. Morris Jr SM. Arginine: beyond protein. Am J Clin Nutr. 2006;83(2):508S-12S.
38. Gokce N. L-arginine and hypertension. J Nutr. 2004;134(10):2807S-11S.
39. Gao L, Zhang JH, Chen XX, et al. Combination of L-Arginine and L-Norvaline protects against

pulmonary fibrosis progression induced by bleomycin in mice. Biomed Pharmacother. 2019;113:108768.

40. Björk I, Lindahl U. Mechanism of the anticoagulant action of heparin. Mol Cell Biochem. 1982;48(3):161-82.
41. Gunther A, Lubke N, Ermert M, et al. Prevention of bleomycin-induced lung fibrosis by aerosolization of heparin or urokinase in rabbits. Am J Respir Crit Care Med. 2003;168(11):1358-65.
42. Franks ME, Macpherson GR, Figg WD. Thalidomide. Lancet. 2004;363(9423):1802-11.
43. Vargesson N. Thalidomide-induced teratogenesis: History and mechanisms. Birth Defects Res C Embryo Today. 2015;105(2):140-56.
44. Tabata C, Tabata R, Kadokawa Y, et al. Thalidomide prevents bleomycin-induced pulmonary fibrosis in mice. J Immunol. 2007;179(1):708-14.
45. Yedinak KC, Lopez LM. Felodipine: a new dihydropyridine calcium-channel antagonist. DICP. 1991;25(11):1193-206.
46. Navadiya K, Tiwari S. Pharmacology, efficacy and safety of felodipine with a focus on hypertension and angina pectoris. Curr Drug Saf. 2015;10(3):194-201.
47. Tanaka K-i, Niino T, Ishihara T, et al. Protective and therapeutic effect of felodipine against bleomycin-induced pulmonary fibrosis in mice. Sci Rep. 2017;7(1):1-12.
48. Gillman P. Tricyclic antidepressant pharmacology and therapeutic drug interactions updated. Brit J Pharmacol. 2007;151(6):737-48.
49. Zaafan MA, Haridy AR, Abdelhamid AM. Amitriptyline attenuates bleomycin-induced pulmonary fibrosis: modulation of the expression of NF-κβ, iNOS, and Nrf2. Naunyn Schmiedebergs Arch Pharmacol. 2019;392(3):279-86.
50. Rodriguez BSQ, Correa R. Gemfibrozil. StatPearls [Internet]: StatPearls Publishing; 2022.
51. Mohammadi Y, Khodayar MJ, Hemmati A, Mansouri E. The preventive role of gemfibrozil on bleomycin-induced lung injury and fibrosis in rats. Jundishapur Journal of Natural Pharmaceutical Products. 2017;12(3 (Supp));e64314.

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