

Abstract

Bleomycin is a chemotherapeutic agent with antibiotic properties, treating cell tumors, gestational trophoblastic diseases, and certain types of lymphoma. This literature review analyzes relevant studies published from 1973 to 2021, focusing on the symptoms of skin toxicity, mechanisms of skin toxicity, and related treatment approaches of skin lesions. Two primary side effects of bleomycin are found to be pulmonary and skin toxicities. Because the skin and lung tissues lack the hydrolase enzyme which rapidly inactivates bleomycin, the drug accumulates in these regions and creates several toxicity symptoms such as hyperpigmentation and flagellate erythema. However, despite findings from existing case reports and in vitro studies, the optimal treatment approach for bleomycin-induced skin toxicity remains unclear, highlighting the need for further research to study the most effective treatment strategies.

Introduction

Bleomycin belongs to the glycopeptide antibiotics, a drug class derived from bacterial species that contains glycosylated peptide cores (Bennett & Reich, 1979). The drug was first discovered in Japan in 1962 by microbiologist Hamao Umezawa. Following several clinical trials, it was approved by the Food and Drug Administration (FDA) to treat several types of disease including cancer in 1975. While previous bleomycin reviews have focused more on lung injury, this is the first time a review has focused on bleomycin-induced skin toxicity such as hyperpigmentation and skin fibrosis. By investigating the underlying mechanisms of the drug, this review contributes to research on preventing bleomycin-induced toxicities and developing more effective chemotherapy approaches.

Methods

In order to address the research question, this review employs a narrative review approach, analyzing and synthesizing existing research such as from clinical reports to in-vitro studies in regards to bleomycin-induced skin toxicities. The studies were selected through research search engines including PubMed and Google Scholar. When using these engines, search terms included "bleomycin," "bleomycin-induced skin toxicity," "side effects," "cutaneous toxicity," "chemical mechanisms," "prevention," and bleomycin chemotherapy." Considering the limited number of studies dedicated to skin toxicity, this review includes studies from the 1900s as well. To assess relevance, studies were included in the literature review if they: were in the language of English, observed results within clinical or simulative laboratory trials, and measured appropriate outcomes such as symptoms associated to skin toxicity including damages to skin tissues, color changes, locations where the skin toxicity appeared, or the period skin toxicity lasted in patients. In contrast, studies were excluded from the literature review if they: lacked measurable outcome data relevant to the research question, did not draw qualitative results from the clinical trials, contained repetitive information from other studies, or only addressed bleomycin-induced lung injury.

Bleomycin-Induced Skin Toxicity: Mechanisms and Potential Approaches to Reduce Skin Toxicity

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Results

A total of six studies were discovered and evaluated in this literature search, addressing symptoms, mechanisms, and treatment approaches related to bleomycin-induced skin toxicity.

Reference	Title	Year	Type of study (case report, case stu clinical trial, in vitro, animal study)	Methods	Major Findings
1	Cutaneous Toxicity of Bleomycin Therapy	1973	Case report	Case report that describes 6 cases of patients showing skin toxicity symptoms such as hyperpigmentation, sclerosis, gangren, following systemic bleomycin exposure	- Hyperpigmentation found primarily on the trunk and small joints - Hyperpigmentation is reversible after drug cessation. - Initial observations suggest hyperpigmentation may be the result of a localized increase in melanogenesis.
2	Bleomycin-induced skin toxicity: is always flagellate erythema?	2016	Case report	Case report that describes a cas diagnosed with Hodgkin's lymph showing skin toxicity symptoms: patchy lesions after bleomycin v administered intravenously	- Skin and lungs have a low concentration of the enzyme hydrolase - Hyperpigmentation, patchy, erythematous skin lesions found on the patient's neck, chest, abdomen, back, and thighs after 10 days of chemotherapy - When topical steroids were applied, they showed improvement, reducing skin toxicity (while corticosteroids were not effective) - Resolved after discontinuation of bleomycin
3	Bleomycin-induced skin toxicity: a case of flagellate dermatitis	2021	Case report	Case report that describes a cas showing bleomycin-induced skin with pruritus, linear, erythematou hyperpigmentation during the ch treatment	- 5 weeks after chemotherapy, pruritic skin lesions that are linear, erythematous, and parallel appear - Pruritus and exoriations improved over 12 weeks - Skin toxicity independent of the dose and route of administration - Permanent hyperpigmentation can occur - Topical/oral corticosteroids used to treat skin lesions
4	Flagellate erythema induced by bleomycin toxicity	2013	Case report	Case report that describes the pi etoposide, and Cisplatin(BEP) regimen. After the third cycle of chemotherapy, he developed asymptomatic erythematous rashes over the back, chest, and thighs, which later subsided with persistenceof hyperpigmentation	A 15-year-old boy diagnosed with an intracranial germ cell tumor underwent surgery and was later treated with a Bleomycin. - Hyperpigmentation, patchy, erythematous skin lesions found on the patient's neck, chest, abdomen, back, and thighs after 10 days of chemotherapy - When topical steroids were applied, they showed improvement, reducing skin toxicity (while corticosteroids were not effective) - Resolved after discontinuation of bleomycin
5	Bleomycin increases steady-state levels of type I collagen, fibronectin and decorin mRNAs in human skin fibroblasts	2000	in vitro	Human dermal fibroblast culture incubated with bleomycin (100nM) Extracellular Matrix (ECM) proteins followed by RNA isolation and N- blotting	- Bleomycin at doses in the range 1 nM to 1 µM exerts toxic effects on fibroblasts, overproducing Extracellular Matrix (ECM) proteins (type I collagen, fibronectin, decorin)
6	Bleomycin enhances the tyrosinase activity of human malignant melanoma cells in culture	1986	in vitro	Investigated the effect of bleomy tyrosinase activity by incubating different periods of time	- Incubation of pigmented human melanoma cells in the presence of bleomycin resulted in increased tyrosinase activity - Histamine stimulates tyrosinase activity in human melanoma cells; histamine supports the bleomycin-induced pigmentation more by vasodilator action and an increased vascular permeability than by directly attacking the melanin-synthesizing cells

Discussion

In terms of mechanism, researchers noted that bleomycin is rapidly inactivated by the enzyme hydrolase. However, because the skin and lungs specifically contain low concentrations of this enzyme, the drug accumulates and causes a direct cellular damage leading to lung and cutaneous toxicities such as flagellate erythema and hyperpigmentaion. This finding establishes a framework for the overall bleomycin mechanism, which better explains the earlier studies. Regarding treatments, researchers reported that oral antihistamines, topical corticosteroids, and oral corticosteroids were required. Considering that Verma et al.'s study considered corticosteroids as ineffective, while Pretorius et al. selected corticosteroids for the treatment, it implies that treatment approaches have been varied in different cases. This difference can be attributed to the limited size of the sample, which highlights that further research is required to identify the effects of corticosteroids on reducing bleomycin-induced hyperpigmentation.

Conclusion

Collectively, these findings suggest that research has progressed from identifying simple symptoms such as hyperpigmentation towards clinical studies addressing underlying mechanisms related to the hydrolase enzyme and more specified symptoms such as liner or patchy erythematous lesions. Overall, the available evidence supports a principle of underlying mechanism where the lack of hydrolase enzyme in the skin creates bleomycin-induced cutaneous toxicity regardless of the amount of dose and routes of administration. However, uncertainty remains regarding the optimal treatment approach for skin lesions such as hyperpigmentation and flagellate erythema. Thus, further research is required to investigate the optimal treatment approach for bleomycin-induced skin toxicity specifically because there are reported cases of hyperpigmentation being permanent.

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