CHAPTER 9

BLEOMYCINE

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Bleomycine is an antitumor, antibacterial and antiviral agent isolated from the actinomycotic soil fungus *Streptomyces verticillus.* It was first recognized by Umezawa and colleagues in 1966.[1] Bleomycine comprises two main subgroups known as bleomycin A and B both of which are subdivided into bleomycin A1-6 and B1-5. Bleomycin A2 and B2 are the main commercially available components and they contain water-soluble glycosylated peptides.[2]

Mechanism of action

Bleomycine acts as an inductor of DNA strand breaks. The exact mechanism of DNA strand scission is unknown. Water-soluble peptides Bleomycin A2 and B2 contain a metal binding core. It is suggested that this complex core plays a critical role of action. Bleomycin chelates metal ions (primarily iron), producing a pseudoenzyme that reacts with oxygen to produce superoxide and hydroxide free radicals that cause oxidative damage to the deoxyribose of thymidilate and other nucleotides, ultimately cleaving the DNA and leading to cell death.[2-4]

This cytotoxic effect of bleomycin is enhanced by coupling the drug with local anesthetics such as dibucaine, tetracain, butacaine, lidocain, procain and ethanol.[5] Local anesthetics disrupt cell membrane and probably cause increased bleomycin uptake and overcome hydrophylic structure of bleomycin,

Similarly electrical stimulation increases the cytotoxic effect of bleomycin.[2] Thus, use of bleomycine is recently started as a part of electrochemotherapy. Electrochemotherapy is a therapeutic procedure which improves membrane permeability and increases drug cytotoxicity. It consists of injection of cytotoxic drugs (like bleomycin or cisplatin) followed by application of current electric pulses directly into tumor lesions on the skin or subcutaneous tissue.[6]

Bleomycin is poorly absorbed after oral administration, so it can only be used intravenously, intramusculary or subcutaneously. Renal excretion is the main metabolism way of this agent.

Adverse effects

Administration route and bleomycin dosage are closely related with severity of side effects. More severe toxicity is noted after total doses greater than 150 mg and with intravenous use. Most severe side effect is pulmonary fibrosis but it is associated with intravenous use.[2] Side effects of intralesional bleomycin are listed in table1.

Dermatological uses

Systemic bleomycin is indicated as adjuvant chemotherapy for treatment of squamous cell carcinoma of head and neck, cervix, penis and skin by Food and Drug Administration (FDA). Although there are no FDA-approved indications for intralesional bleomycine usage, it can be used as an off-label drug in various dermatological conditions. The bleomycin hydrolase enzyme which is known to inactivate bleomycin is found in all body tissues but in very small amounts in skin. Thus, after intralesional injection of bleomycin, a significant amount of the active drug is available for action at site, and so even a small amount is enough for treatment of various dermatologic diseases.[7]

Dermatological diseases in which bleomycin can be used effectively are shown below.

Warts

Bleomycin injection for warts has been investigated in several clinical studies. The cure rates have ranged from 0% to 100%, and most of these studies showed intralesional route to be safe and effective in warts, particularly in palmo-plantar and periungual regions.[2, 7-10] Bleomycin was diluted with distillated water for intralesional application and its concentration varied between 0.05% and 2% in these studies.

Soni et al. applied 1 mg/ml intralesional bleomycin diluted with distillated water and 2% lidocain to 85 recalcitrant periungual or palmoplantar warts. After 2 weeks of treatment, bleomycin was injected for the second time if residual warts persisted. Complete resolution was shown in 82 (96.47%) of 85 lesions after one or two injections within 12 weeks whereas it was only 8 of 72 in the placebo group.[7]

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