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Bleomycin Chemotherapy for Oral Leukoplakia

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1. Introduction

Over the years potentially malignant disorders like oral leukoplakia (OL) and oral erythroplakia (OE) are associated with dysplastic cellular changes and hence carry a risk of undergoing malignant transformation leading to oral cancer (OC) (1). Numerous surgical and nonsurgical modalities have been used for treatment of OL (2). Some of the non-surgical modalities used for the treatment of OL include photodynamic therapy, beta-carotene, lycopene, or vitamin A (2, 3). Bleomycin a chemotherapeutic agent has also been used for treatment of leukoplakia and other malignant lesions (4-8). Apart from topical application report intralesional injection of bleomycin into OL lesion has been performed with good results (9). Another study suggested the delivery of bleomycin into head and neck tumors using iontophoresis (10). The purpose of this article is to provide a brief review of the use of bleomycin in the treatment of oral cancer and precancerous lesion (Table 1).

2. Biological Properties of Bleomycin

The bleomycin is glycopeptide-derived antibiotic isolated from streptomyces (11). The biological action of bleomycin is through a sequence-selective, metal-dependent oxidative cleavage of DNA and RNA in the presence of oxygen. It can mediate the oxidative degradation of all major classes of cellular RNAs and inhibition of DNA synthesis (11).

3. Bleomycin in Dermatology

Studies have suggested intralesional injection of bleomycin to be highly effective in treatment of warts (12). Off-label use of intralesional bleomycin is another primary and/or adjunctive therapy for different cutaneous lesions dermatology as several types of cutaneous malignancies, telangiectasias, vascular malformations, hemangiomas, and lesions of leishmaniasis cutisand condyloma acuminate (13). Studies have also suggested intralesional bleomycin to be more effective in treatment of warts when compared to surgical modalities like cryotherapy (14). Recent research has revealed that bleomycin is a reliable and safe treatment modality for warts resistant to other therapeutics (15).

4. Bleomycin in Cancer Treatment

Bleomycin along with Adriamycin, vinblastine and dacarbazine is the standard chemotherapy regimen for Hodgkin's, and non-Hodgkin's lymphoma disease squamous cell cancers, sarcoma, melanoma, and testicular cancer. Also it is used to treat malignant pleural effusion and Leukemias (16). Bleomycin is found to concentrate more in lymphoid tissue and does not cause excessive myelosuppression, thus is the preferred agent in chemotherapeutic regimens for non hodgkins lymphoma also (17). Bleomycin is one of the important drugs in induction chemotherapy for testicular cancer (18). Bleomycin also is a key component in the chemotherapy regimens for cervical and ovarian cancer (19, 20).

5. Bleomycin in Oral Leukoplakia

Oral leukoplakia is defined as "a predominantly white lesion of the oral mucosa that cannot be characterized as any other definable lesion. It is the most common potentially malignant disorder". A risk factor for malignant transformation of OL is Candida invasion. It may be associated with certain clinical characteristics such as lesion

Table 1. Displaying Studies Conducted by Researchers Using Bleomycin in Oral Cancer and Precancer Patients

Researchers and Year	Study Subjects	Drug Administration	Results
Hammersley N et al. 1985	6 oral leukoplakia subjects	0.5% bleomycin topical application	Significant reduction in clinical size and dysplastic features
Malmstrom M et al. 1988	10 oral leukoplakia subjects	Topical bleomycin	Epithelial dysplasia resolved in 5 out 10 study subjects
Tashiro H et al. 1988	11 oral cancer patients	Topical bleomycin and radiotherapy	One subject had early recurrence and three had recurrences after 2 years
Wong F et al. 1989	12 (2 subjects were exclude from analysis)	0.5% topical bleomycin	Subjects treated with 0.5% bleomycin showed decrease in the clinically observed thickness
		1% topical bleomycin	Subjects treated with 1% bleomycin showed complete resolution of lesion
Epstein JB et al. 1994	22 oral leukoplakia subjects	1% topical bleomycin	Significant reduction in clinical size of the lesion and reduction in dysplasia
Epstein JB et al. 1998	19 oral leukoplakia subjects	1% topical bleomycin	75% of study subjects showed resolution of dysplasia in follow-up biopsy

type, size, and site, dysplasia, and tobacco use. The prevalence of OL is approximately 2% with an annual malignant transformation of approximately 1% (21).

Warnakulasuriya et al. listed the overall risk factors for malignant transformation in leukoplakia as follows: female gender, long duration of leukoplakia, leukoplakia in nonsmokers (idiopathic leukoplakia), location on the tongue and/or floor of the mouth, nonhomogeneous type, presence of Candida albicans and presence of epithelial dysplasia (21).

One of the earliest reported studies using bleomycin was carried out by Hammersley N et al. wherein a 0.5 per cent (w/v) solution of bleomycin sulphate in dimethyl sulphoxide was used for 12 to 15 days on six subjects (8). Significant clinical and histopathological improvements were observed. After their study, using bleomycin Malmstrom M et al. stated that clinically visible changes can be appreciated only three months after the application of bleomycin therapy but once the lesions disappear, the recurrence rate is less than the cases which have been treated surgically (7). Tashiro H et al. used non-surgical technique combining topical application of bleomycin and radiotherapy for oral cancer cases (22). They concluded that the apparent cure brought about by this conservative modality may harbor latent evidence of malignancy (22).Wong F and his colleagues from their study using bleomycin on oral leukoplakia observed that when 0.5% of topical bleomycin was used, it caused reduction in clinically observed thickness of oral leukoplakia lesions (23). However, they observed that when 1% topical bleomycin was used, complete resolution of the lesion was observed (23). Epstein JB and his fellow researchers observed reduced histopathological evidence of dysplasia in 75% of study subjects with oral leukoplakia (24).

Besides studies, few case reports have been also published wherein bleomycin has been used to successfully manage oral carcinoma (25, 26). Recent studies by Strojan P and his associates revealed that a combination of radiotherapy and chemotherapy (Vinblastine, Methotrexate, and Bleomycin) was a very good alternative in inoperable verrucous carcinoma of the head and neck region (27). The research trends suggest that the recent studies are more focused on using combination therapies involving bleomyicin rather than single drug regimens.

6. Bleomycin Toxicity

The major toxic effect of bleomycin is on the pulmonary system (28). Bleomycin induced pneumonitis occurs in nearly 20% of cancer patients who are administered regimens containing bleomycin (29). With predisposing factors like pulmonary a disorders renal disorders and old bleomycin toxicity can be fatal (30, 31). However several cases have been reported wherein the toxicity has been reversed by administering high dose of steroids (32).

To conclude, in this article we have made an attempt to briefly present the therapeutic actions of bleomycin with special emphasis on the management of oral cancer and pre-cancer with bleomycin. The research trend in this field shows a combination therapy involving modality life radiotherapy show more promise in treatment of cancer rather than single drug therapy.

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