Content available at: https://www.ipinnovative.com/open-access-journals

Indian Journal of Clinical and Experimental Ophthalmology

Journal homepage: www.ijceo.org

Editorial

Bleomycin in ophthalmology: An update

Rajendra Prakash Maurya [1,*]

[1] *Regional Institute of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, Uttar Pradesh, India*

ARTICLE INFO

Article history:
Received 22-06-2022
Accepted 26-06-2022
Available online 29-06-2022

Season Greetings !!

1. Introduction

Bleomycin is a drug of diverse mechanism of action. It is a DNA cleaving antibiotic, which was first isolated in 1966 by Umezawa from a soil fungus Streptomyces verticillus. It is an anti-cancer (antineoplastic or cytotoxic) chemotherapeutic drug. It is a mixture of two copper-cheating peptides, bleomycin A_2 and B_2, that only differ in their terminal amino acid. The main mechanism of action is inhibition of DNA synthesis and it plays an important role in the treatment of many cancers like Hodgkin disease and testicular cancers. It also has a sclerosing effect on the vascular endothelium and is used in treating vascular anomalies. [1]

2. Mechanism of Action

Bleomycin's cytotoxicity develops from its ability to cause oxidative damage to the deoxyribose of thymidylate and other nucleotides, leading to single or double strand breaks in DNA. Bleomycin causes oxidative damage and cleaves the DNA by generation of free radicals, which forms when its metal binding core is oxidised. Metallobleomycin complexes can be activated by flavin enzyme, NADPH-CYP450. Bleomycin binds to DNA and the activated metal-drug complex generates free radicals and causes strand breaks in DNA and hence, causes cell death. Bleomycin blocks the cell cycle at G_2 phase causing accumulation of cells in the G_2 phase. It causes apoptosis in actively dividing cells and also has a sclerosing effect on the vascular endothelium, which makes it useful in treating vascular neoplasms. Its other mechanism of action includes degradation of cellular RNA and induction of tumour necrosis factor.

Bleomycin is degraded by specific hydrolase enzyme found in many tissues, including liver. Hydrolase activity is low in skin and lung, leading to serious toxicity in these organs. Resistance against bleomycin can be due to high levels of hydrolase activity in the cells, decreased uptake of drug, repair of strand breaks, or drug inactivation by thiols or thiol-rich proteins. [2]

3. Pharmacokinetics

Bleomycin can be used systemically or locally like it can be administered as i.v, i.m or s/c injections or can be given intralesionally in ophthalmic conditions like hemangiomas or lymphangiomas and it can also be instilled into the bladder for local treatment of bladder cancer and intrapleurally for malignant pleural effusion. It poorly crosses the blood-brain barrier due to its high molecular weight. Elimination $t_{1/2}$ of drug is about 3 hours and majority of the drug is excreted through urine. It should be used with caution in patients with renal impairment and low

* *Corresponding author.*
E-mail address: editorijceo@gmail.com (R. P. Maurya).

https://doi.org/10.18231/j.ijceo.2022.034

doses of drug should be used if clearance is less than 60 ml/min.

4. Therapeutic uses

Bleomycin is given by i.v, i.m or s/c route weekly or twice weekly. Systemic use of bleomycin has been approved by FDA in many conditions like squamous cell carcinoma of the head and neck, cervix, penis and skin, Hodgkin's and non-Hodgkin's lymphoma, testicular malignant tumours and other malignancies. Myriad regimens are employed clinically in which bleomycin dose is expressed in units. Total dose exceeding 250mg is only used in treatment of high-risk testicular cancer and should be used with caution due to the risk of developing pulmonary fibrosis. Bleomycin can be instilled in the pleural space for treating malignant pleural effusion. It is highly effective against germ cell tumours of the testis and ovary. It is used in combination with cisplatin and vinblastine or cisplatin and etoposide for managing testicular cancer. It is the component of standard ABVD treatment regimen for Hodgkin disease.

Intralesional bleomycin injections (IBI) can be used to treat hemangiomas and lymphangiomas in various anatomical locations due to its sclerosing effect on the vascular endothelium, which causes endothelial cell detachment with inflammation resulting in fibrosis and involution.[3–5] A study indicates that 56.2% of congenital lymphatic and vascular malformations of the head and neck showed 70-100% regression after treatment with IBI, suggesting higher success rate.[5] Basal cell carcinoma, Kaposi sarcoma, keratoacanthoma and skin metastasis of malignant melanoma can be treated with IBIs as well.[6] Bleomycin as a sclerosing agent can be used intralesionally for the treatment of orbital lymphangiomas (both refractory and non-refractory),[7,8] non-orbital lymphangiomas[9] and lymphangiomas of the face, neck and thorax regions.[10]

IBI is an alternative in the treatment of periocular capillary hemangiomas refractory to conventional modalities like corticosteroids, radiotherapy or debulking surgery. For periocular capillary hemangioma in infants, monthly IBI (0.5mg/kg) is used and is diluted with normal saline which is equivalent to the volume of the lesion. For orbital lymphangiomas, bleomycin solution is prepared by mixing 2% lignocaine along with normal saline in a ratio of 1:1. Lignocaine reduces the discomfort postoperatively and also increases entry of drug into the cell by making it more permeable. Total cumulative dose doesn't exceed 10 mg for any patient that is way too less than what is required for causing pulmonary fibrosis (250mg).[11] Risk of developing pulmonary fibrosis after IBIs is small.[12] Bleomycin is an effective intralesional sclerosant and is very useful as the sole or adjunct treatment in superficial ocular adnexal lymphatic malformations.[13,14]

It has good safety profile and minimal adverse effects as a sclerosant. In superficial ocular adnexal lesions, imaging guidance is also not esssential for IBIs. There is also minimal chances of recurrence of lymphangiomas following treatment wih IBIs.[15–18] Therefore, IBIs can be considered as a safe first line agent for the treatment of orbital lymphangiomas.[19]

5. Adverse Effects of Bleomycin Therapy

Bleomycin causes little myelosuppression but it can cause a range of cutaneous toxicity which can manifest as hyperpigmentation, hyperkeratosis, erythema, ulceration and rarely, Raynaud's phenomenon and flagellate dermatitis. Most serious complication that can occur with systemic bleomycin therapy is pulmonary fibrosis. 5-10% of patients develops pulmonary toxicity and 1% die of this complication. Pulmonary toxicity is related to cumulative dose of bleomycin therapy; risk is higher if the total dose is greater than 250mg, in patients of more than 40 years of age, in those whose CL_{Cr} is less than 80 ml/min and in those with underling pulmonary disease. Pulmonary fibrosis is the most important dose-dependent side effect of systemic therapy but it is not reported with intralesional bleomycin sclerotherapy. Other side effects are hyperthermia, headache, nausea, vomiting and peculiar acute fulminant reaction seen in 1% of patients with lymphomas or testicular cancer.

Intralesional bleomycin injection/sclerotherapy has more local side effects like erythema, swelling, pain and occasionally fever. Bleeding, ulceration, cellulitis, local skin necrosis, eschar formation, hypopigmentation, transient alopecia and flu-like symptoms may also occur. Lymphangitis, flagellate hyperpigmentation and Raynaud's phenomenon are very rare. Systemic steroids (1mg/kg body weight) for 1 week can be given after IBIs to reduce inflammation.

Conflicts of Interest

None.

References

1. Umezawa H. Recent study on biochemistry and action of Bleomycin. In: Carter SK, Crook ST, Umezawa H, editors. Bleomycin: Current Status and New Developments. Academic Press; 1978. p. 15–20.
2. Brunton LL, Hilal-Dandan R, Knollmann BC. Goodman & Gilman's: The Pharmacological Basis of Therapeutics. 13th ed. McGraw Hill;.
3. Pienaar C, Graham R, Geldenhuys S, Hudson DA. Intralesional bleomycin for the treatment of hemangiomas. *Plast Reconstr Surg*. 2006;117(1):221–6.
4. Muir T, Kirsten M, Fourie P, Dippenaar N, Ionescu GO. Intralesional bleomycin injection (IBI) treatment for haemangiomas and congenital vascular malformations. *Pediatr Surg Int*. 2004;19(12):766–73.
5. Mathur NN, Rana I, Bothra R, Dhawan R, Kathuria G, Pradhan T. Bleomycin sclerotherapy in congenital lymphatic and vascular malformations of head and neck. *Int J Pediatr Otorhinolaryngol*. 2005;69(1):75–80.
6. Saitta P, Krishnamurthy K, Brown LH. Bleomycin in dermatology. *Dermatol Surg*. 2008;34:1299–313.

7. Gooding C, Meyer D. Intralesional bleomycin: a potential treatment for refractory orbital lymphangiomas. *Ophthalmic Plast Reconstr Surg*. 2014;30(3):65–72.
8. Baskin D, Tander B, Bankaoğlu M. Local bleomycin injection in the treatment of lymphangioma. *Eur J Pediatr Surg*. 2005;15(6):383–6.
9. Kumar V, Kumar P, Pandey A, Gupta DK, Shukla RC, Sharma SP, et al. Intralesional bleomycin in lymphangioma: an effective and safe non-operative modality of treatment. *J Cutan Aesthet Surg*. 2012;5(2):133–6.
10. Rozman Z, Thambidorai RR, Zaleha AM, Zakaria Z, Zulfiqar MA. Lymphangioma: is intralesional bleomycin sclerotherapy effective? *Biomed Imaging Interv J*. 2011;7(3):e18.
11. Macintosh PW, Yoon MK, Fay A. Complications of intralesional bleomycin in the treatment of orbital lymphatic malformations. *Semin Ophthalmol*. 2014;29(5-6):450–5.
12. Ionescu G, Mabeta P, Dippenaar N, Muir T, Fourie P, Shelver G. Bleomycin plasma spill-over levels in paediatric patients undergoing intralesional injection for the treatment of haemangiomas. *S Afr Med J*. 2008;98(7):539–40.
13. Bothra N, Panda L, Sheth J, Tripathy D. Role of intralesional bleomycin sclerotherapy as the sole or adjunct treatment of superficial ocular adnexal lymphatic malformations. *Eye (Lond)*. 2018;32(1):152–5.
14. Suzuki Y, Obana A, Gohto Y, Miki T, Otuka H, Inoue Y. Management of orbital lymphangioma using intralesional injection of OK-432. *Br J Ophthalmol*. 2000;84(6):614–7.
15. Raichura ND, Alam MS, Noronha VO, Mukherjee B. A prospective study of the role of intralesional bleomycin in orbital lymphangioma. *J AAPOS*. 2017;21(2):146–51.
16. Giguère CM, Bauman NM, Smith RJ. New treatment options for lymphangioma in infants and children. *Ann Otol Rhinol Laryngol*. 2002;111(12 Pt 1):1066–75.
17. Zhong PQ, Zhi FX, Li R, Xue JL, Shu GY. Long-term results of intratumorous bleomycin-A5 injection for head and neck lymphangioma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod*. 1998;86(2):139–44.
18. Paramasivam S, Fay A, Fifi J, Berenstein A. O-015 image guided bleomycin sclerotherapy for orbital lymphatic malformation. *J Neuro Intervent Surg*. 2014;6(1):8–9.
19. Nuruddin M, Roy SR, Mudhar HS. Results of Intralesional Bleomycin Sclerotherapy for Treatment of Orbital Lymphangiomas at a Tertiary Eye Care Centre in Bangladesh. *Ocul Oncol Pathol*. 2019;5(6):412–7.

Author biography

Rajendra Prakash Maurya, (MBBS, MS, Ph.D), Editor in Chief IJCEO, Associate Professor & I/c Orbit, Ocular Oncology and Oculoplasty Unit Regional Institute of Ophthalmology, Institute of Medical Sciences, Banaras Hindu University, Varanasi, (UP), India E-mail: editorijceo@gmail.com, mauryarp_bhu@yahoo.com
https://orcid.org/0000-0001-9343-6003

Cite this article: Maurya RP. Bleomycin in ophthalmology: An update. *Indian J Clin Exp Ophthalmol* 2022;8(2):174-176.