DRUG NAME: Bleomycin

SYNONYM(S): NSC-125066;[1] BLM²; Bleo

COMMON TRADE NAME(S): BLENOXANE®, generic available

CLASSIFICATION: Antitumour antibiotic

Special pediatric considerations are noted when applicable, otherwise adult provisions apply.

MECHANISM OF ACTION:

Bleomycin causes DNA strand scission through formation of an intermediate metal complex requiring a metal ion cofactor such as copper or iron.[2] This action results in inhibition of DNA synthesis, and to a lesser degree, in inhibition of RNA and protein synthesis.[3] The drug is cell-cycle specific for G phase, M-phase and S phase.[1]

PHARMACOKINETICS:

Interpatient variability	no information found	
Distribution	mainly in the skin, lungs, kidneys, peritoneum and lymphatics	
	cross blood brain barrier?	no
	volume of distribution[1]	20 L
	plasma protein binding[1]	less than 10%
Metabolism	activated by microsomal reduction, degraded by hydrolase found in multiple tissues especially in liver and kidneys[1]	
	active metabolite(s)	no information found
	inactive metabolite(s)	no information found
Excretion	renal: 45-70% in first 24 h[4]	
	urine	60-70% active drug (less than 20% in patients with moderate renal impairment [creatinine clearance less than 35 mL/min])
	feces	no information found
	terminal half life[2]	2-4 h (may be prolonged with renal dysfunction); 3 h (intrapleural); 5 h (intraperitoneal)
	clearance[2]	3 L/h/m²
Gender	no information found	
Elderly	no information found	
Children[5]	terminal half life	3 h
	clearance	2.5 L/h/m²
	renal clearance	65%
Ethnicity	no information found	

Adapted from standard references[3,6] unless otherwise specified.

USES:

Primary uses:
*Cervical cancer
*Larynx and paralarynx
*Lymphoma, Hodgkin's
*Lymphoma, non-Hodgkin's
*Malignant pleural effusion
*Penile cancer
*Renal cancer
*Soft tissue sarcoma
*Testicular cancer
*Vulva cancer
*Lung cancer

*Health Canada approved indication

Other uses:
Dysplastic oral leukoplakia[7]
Head and neck[6]
Kaposi's sarcoma[6]
Melanoma[8]
Mycosis fungoides[8]
Osteosarcoma[8]
Skin cancer[8]
Thyroid cancer[8]
Trophoblastic, gestational[8]
Cystic craniopharyngioma[9]

SPECIAL PRECAUTIONS:

Contraindicated in: patients who have a history of hypersensitivity reaction to bleomycin.[3]

Use with caution in patients[3,6,8]: with compromised pulmonary function, with compromised renal function**,** with an age greater than 40 years,[10] receiving concomitant chest radiation, receiving concomitant administration of cisplatin, cyclophosphamide, methotrexate or doxorubicin, receiving positive fluid balance during prolonged surgical procedures and who smoke. These are all risk factors that can predispose the patient to bleomycin pulmonary toxicity (BPT), which can be severe and life threatening.
A cumulative dose of greater than 450 units of bleomycin is also a known risk factor for developing BPT.

Carcinogenicity: Bleomycin is carcinogenic in animals.[3]

Mutagenicity: Bleomycin is not found to be mutagenic when using the Ames test[8], but has been shown to be mutagenic *in vitro* and *in vivo* using other mutation tests.[6]

Fertility: no information found.

Pregnancy: FDA Pregnancy Category D. There is positive evidence of human fetal risk, but the benefits from use in pregnant women may be acceptable despite the risk (e.g., if the drug is needed in a life-threatening situation or for a serious disease for which safer drugs cannot be used or are ineffective).[11]

Breastfeeding is not recommended due to the potential secretion into breast milk.[12]

SIDE EFFECTS:

The table includes adverse events that presented during drug treatment but may not necessarily have a causal relationship with the drug. Because clinical trials are conducted under very specific conditions, the adverse event rates observed may not reflect the rates observed in clinical practice. Adverse events are generally included if they were reported in more than 1% of patients in the product monograph or pivotal trials, and/or determined to be clinically important.

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
allergy/immunology[4]	hypersensitivity reactions (fever, anaphylaxis, eosinophilic pulmonary infiltrates)
blood/bone marrow	anemia (mild)

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
febrile neutropenia	leukopenia
	myelosuppression (uncommon, mild)
	thrombocytopenia
cardiovascular (general)	edema of hands and feet
	hypotension[2]
	myocardial infarction (rare)
	phlebitis (uncommon)
	thrombotic microangiopathy (rare)
constitutional symptoms	chills (common)
	fever (50%) less frequent with continued use[8]
	malaise
	weakness, general
	weight loss (common)
dermatology/skin	*extravasation hazard:* rare
	alopecia, diffuse
	desquamation[4]
	erythema
	facial flushing[2]
	hyperkeratosis of hands and nails
	hyperpigmentation especially in creases and folds in the areas of trauma[2] (frequent)
	hypoesthesia progressing to hyperesthesia
	ichthyosis, peeling and bleeding
	induration[13]
	paresthesia
	prorates
	rash on pressure areas and abdominal skin creases (8%)
	Raynaud's phenomenon[4] (rare)
	scaling[2]
	stomatitis
	striae
	tenderness of skin
	thickening of skin[2]
	ulcerations, tongue, lips (rare)
	urticaria
	vesiculation

ORGAN SITE	SIDE EFFECT
Clinically important side effects are in ***bold, italics***	
gastrointestinal	*emetogenic potential:* Low Moderate
	anorexia (common)
	mucositis (30%)
	nausea
	stomatitis (30%)
	vomiting (common)
hepatic	hepatic toxicity (rare)[8]
neurology	aggressive behaviour (rare)
	cerebrovascular accident (rare)
	cerebral arteritis (rare)
	disorientation (rare)
ocular/visual	periorbital edema[4]
pain	chest pain[4], acute, suggestive of pleuropericarditis (rare)
	myalgias[2] (less frequent)
pulmonary	bronchospasm[4]
	dyspnea
	pleuropericarditis (rare)[8]
	pneumonitis (10%)
	pulmonary fibrosis (1%)
	rales
renal/genitourinary	cystitis (rare)
	hematuria (rare)
	hemorrhagic cystitis (rare)
	renal toxicity (rare)

Adapted from standard references[3,6] unless specified otherwise.

Dermatologic effects are the most frequent adverse effects of bleomycin, occurring in 50% of patients[3] usually occurring 2-4 weeks after initiation of therapy.[8] Adverse mucocutaneous effects including erythema, rash, striae, vesiculation, hyperpigmentation, and tenderness of skin usually develop in the second or third week of bleomycin therapy. Mucocutaneous effects appear to be dose related, usually occurring after 150-200 units of bleomycin. Discontinuation of therapy due to these toxicities occurs in about 2% of patients.[6]

Febrile reactions are seen in 50% of patients treated with bleomycin given IV and in 25% of patients where bleomycin is given IM. This reaction can be prevented by hydrocortisone premedication. Pre-treatment with antipyretics or antihistamines can also be used,[3] but have not produced uniform results in reducing bleomycin associated fever.[6]

Hypersensitivity reactions occur in 1% of lymphoma patients receiving bleomycin. This anaphylactic reaction can include hypotension, fever, chills, mental confusion, and wheezing.[6] This idiosyncratic reaction can occur immediately or be delayed for several hours. This reaction usually occurs after the first or second dose. The manufacturer

suggests using a test dose of 2 units or less for the first 2 doses.[14] If no acute reaction occurs after 2 to 4 hours, then regular dosing may commence.[1,4] The use of a test dose is not universally accepted.[15-17]

Respiratory effects are the most serious side effects for bleomycin.[6] Bleomycin pulmonary toxicity BPT occurs in 10% of treated patients.[3] In approximately 1%, the non-specific pneumonitis induced by bleomycin progresses to pulmonary fibrosis and death. Non-productive cough, dyspnea, basal rales, pleuritic chest pain and fever are frequently first signs of toxicity.

Pulmonary fibrosis from bleomycin can develop insidiously during treatment.[18] Patients should be questioned carefully for new dry unproductive cough or new respiratory limitation of exercise tolerance at each visit. Persistence of either of these symptoms for longer than one week without other explanation, such as infection, should prompt consideration of discontinuation of the bleomycin. Some authors have recommended serial measurement of carbon monoxide diffusing capacity by pulmonary function testing, however, this has not proved to be a reliable predictor of bleomycin toxicity and its use must be individualized. A normal chest x-ray is unreliable to exclude BPT.[10,18]Identification of patients with bleomycin induced pulmonary toxicity can be very difficult due to the non-specific signs and symptoms.[6] Treatment includes corticosteroids for pneumonitis to prevent pulmonary fibrosis and antibiotics for infectious pneumonitis.

See Special Precaution section for risk factors which can predispose a patient to BPT. In addition to these risk factors oxygen therapy after treatment with bleomycin is considered a risk factor to developing BPT.

The following recommendations have been developed regarding the use of oxygen therapy in patients who have been treated with bleomycin[10]:

1. Although the evidence is inconsistent with regards to the relationship between supplemental oxygen therapy and bleomycin lung toxicity, patients should not be denied oxygen therapy if hypoxia is documented or anticipated.
2. If supplemental oxygen is required, the lowest FIO_2 that maintains adequate tissue oxygenation (as measured by arterial blood gasses or pulse oximetry) should be provided.
3. Preoperative anaesthesia consultation should be mandatory for patients with a history of bleomycin therapy.
4. Recreational use of high flow oxygen (e.g., scuba diving) should be discouraged.
5. Patients should be encouraged to carry wallet cards or wrist bracelets alerting caregivers to possible toxicity associated with oxygen therapy.

(More information under "A Guideline for Oxygen Therapy for Patients who have Received Bleomycin Systemic Therapy" after References)

INTERACTIONS:

AGENT	EFFECT	MECHANISM	MANAGEMENT
cisplatin[1]	may increase risk of bleomycin toxicity	reduced bleomycin elimination	monitor for bleomycin toxicity
digoxin[19]	may decrease digoxin levels	changes to intestinal mucosa may decrease digoxin absorption	monitor for decrease in pharmacological effect of digoxin
phenytoin[19]	may decrease phenytoin levels	decreased absorption, increased metabolism of phenytoin	monitor serum levels of phenytoin
vincristine[8]	sequential administration of vincristine given before bleomycin may improve bleomycin efficacy	vincristine arrests cells in mitosis so that they are more susceptible to the actions of bleomycin	can be used for therapeutic advantage

SUPPLY AND STORAGE:

Injection: Supplied as single dose vials containing 15 units of bleomycin.[3] Bleomycin is a mixture of peptides and should be described in units rather than mg.[2] **Mayne Pharma's formulation contains 1.5-2.0 units of bleomycin per milligram**, while Bristol Laboratories' formulation contains 1 unit of bleomycin per milligram.[20] Store vials between 2-8°C, and protect from light. Intact vials are stable for 28 days at room temperature.[21]

SOLUTION PREPARATION AND COMPATIBILITY:

For basic information on solution preparation and compatibility, see Chemotherapy Preparation and Stability Chart in Appendix.

Additional information:
Reconstitution is based on administration.

- For IM or SC injection dissolve the contents of the vial in 1-5mL of either SWI or NS to give a solution of 3-15 units/mL.[3]
- For IV or intra-arterial administration dissolve the contents of the vial in 5-10 mL SWI or NS to give a solution of 1.5-3 units/mL.
- For intra-pleural administration dissolve the contents of 1-8 vials (15-120 units) in 100 mL of either NS or D5W.
- For intra-peritoneal administration dissolve the contents of 4-8 vials (60-120 units) in 100 mL of NS.

Compatibility: consult detailed reference

PARENTERAL ADMINISTRATION:

BCCA administration guideline noted in ***bold***, ***italics***

Subcutaneous[1]	has been given
Intramuscular[1]	has been given
Direct intravenous	give slowly over 10 min
Intermittent infusion	***in 50 mL over 10-15 min***
Continuous infusion	has been given
Intrapericardium[2]	has been given
Intraperitoneal[3]	has been given
Intrapleural[21]	***by physician only***
Intrathecal	no information found
Intra-arterial[1]	has been given
Intravesical[5]	has been given
Intratumoral[1,9]	instilled into Ommaya reservoir

There is some evidence that administration of bleomycin by continuous infusion over 24 hours rather than intermittently may be associated with less pulmonary and idiosyncratic toxicity, although mucocutaneous toxicity may be increased.[8]

DOSAGE GUIDELINES:

Refer to protocol by which patient is being treated. Numerous dosing schedules exist and depend on disease, response and concomitant therapy. Guidelines for dosing also include consideration of absolute neutrophil count

(ANC). Dosage may be reduced, delayed or discontinued in patients with bone marrow depression due to cytotoxic/radiation therapy or with other toxicities.

Adults:

BCCA usual dose noted in ***bold, italics***

Intravenous: Cycle Length:

1-3 weeks:	***10 units/m² (range 5-10 units/m^2) IV for one dose on day 1 (total dose per cycle 10 units/m^2 [range 5-10units/m^2])***
2 weeks:	***10 units/m^2 IV for one dose on day 8 (total dose per cycle 10 unit/m^2)***
3 weeks:	***30 units IV for one dose on day 1 (total dose per cycle 30 units)***
3 weeks	***30 units IV for one dose on day 2, day 9, day 16 (total dose per cycle 90 units)***
4 weeks:	***10 units/m² IV for one dose on day 8 (total dose per cycle 10units/m²)***
4 weeks:	***10 units/m^2 IV for one dose on day 1 and day 15 (total dose per cycle 20units/m^2)***

Dosage in myelosuppression: modify according to protocol by which patient is being treated; if no guidelines available, refer to Appendix 6 "Dosage Modification for Myelosuppression"

Dosage in renal failure[3]:

Creatinine clearance (mL/min)	Dose
>50	100%
10-50	75%
<10	50%

Calculated creatinine clearance = $\frac{N^* \times (140 - \text{Age}) \times \text{weight (kg)}}{\text{Serum Creatinine in } \mu\text{mol/L}}$

* For males N = 1.23; for females N=1.04

Dosage in hepatic failure: no adjustment required

Dosage in dialysis[1] : not effectively hemodialyzed

Intra-arterial: 30-60 u once or twice a week, to a total recommended dosage of 300 u.[3] Intra-arterial bleomycin serum concentration peaks were reported to be three times higher then levels from comparable IV doses.[1]

Intrapleural[3]: 50-60 u in 100 mL NS or D5W. (not exceeding 1 unit/kg or 40 units/m² in geriatric patients).

Intra-tumoral[1]: small doses are diluted in a minimal volume of NS and combined with lidocaine. Local skin reactions and soft tissue toxicity may be severe.

Intravesical[1]: 30-120 u in 30-60 mL water.

Maximum lifetime dose[8] : 400 units (less for patients with renal or pulmonary function impairment) due to the risk of pulmonary toxicity. Doses greater than this must be given with great caution. Count intraperitoneal and intrapleural doses as half. For bleomycin given intravesically the systemic absorption is minimal.

Children[5]:

10-20 units/m² IV by bolus or infusion, IM, or SC.

Intrapleural and intravesicular administration are used.

Intratumoral dosing is 2.5-5 units instilled into Ommaya reservoir three times weekly aiming for 12 doses.[9,22]

Dosage in renal failure: 45-65% dosage reduction has been recommended for children with a creatinine clearance of less than 30 mL/min/m².

TOPICAL ADMINISTRATION:

Oral, topical administration[1,7]: 1% bleomycin in dimethylsulfoxide applied once daily for fourteen consecutive days. The solution is applied directly to the lesions on the oral mucosa.

Topical application[1]: 1% ointment in petrolatum applied to affected area followed by an occlusive dressing.

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Bleomycin Associated Lung Toxicity. A Guideline for Oxygen Therapy for Patients who have Received Bleomycin Systemic Therapy.

Effective date: *27 July 2000*
Prepared by: *Dr. Judy Sutherland on behalf of GU Tumour Group*
Approved by: *Provincial Systemic Program Committee*

The objective of this guideline is to provide recommendations for oxygen therapy based on the quality of available published evidence relating bleomycin pulmonary toxicity (BPT) to supplemental oxygen therapy. The diagnosis and treatment of BPT have been reviewed elsewhere and will not be reported in this guideline. A MEDLINE literature search of all published abstracts, case reviews and clinical trials using the search terms "Bleomycin" (adverse effects, poisoning, toxicity) and "Lung diseases" (chemically induced) was undertaken. Documents retrieved were limited to those published in English and related to human exposure. Seventy-three publications since 1970 were identified and reviewed. The strength of the data were graded according to standard criteria.[1]

Bleomycin has been used in combination chemotherapy for patients with germ cell tumours, Hodgkin's disease and non-Hodgkin's lymphoma for more than 20 years. Overall response rates of 50-90% have been achieved. Reported toxicities have included mucositis, hypersensitivity reactions, skin rashes and BPT.[2-4] The reported incidence of non fatal BPT is dependent on the diagnostic criteria used but appears to be 5-10% and fatal BPT has been reported in approximately 2% of treated cases.[5,6] Pulmonary toxicity may occur in the form of acute pneumonitis, chronic pulmonary fibrosis or acute respiratory distress syndrome (ARDS) which is most commonly seen in the postoperative setting.[7,8] Risk factors that have been associated with BPT include age >40 years, cumulative dose of >450 units, renal failure, concomitant administration of cisplatin, cyclophosphamide, methotrexate and doxorubicin, chest irradiation, and positive fluid balance during prolonged surgical procedures.[5,6] Animal studies have demonstrated that supplemental oxygen may be an additional risk factor for lung toxicity [9], but human data based on case reports, and retrospective reviews are less clear. Multivariate analyses in two large retrospective reviews have not identified high flow oxygen as an additional risk factor for BPT.[10,11] Prospective randomized studies evaluating pulmonary morbidity in bleomycin treated patients have not been reported.

The vast majority of the data relating BPT to oxygen therapy has been obtained from patients undergoing general anesthesia and surgical resections following chemotherapy with multiagent regimens containing bleomycin. Very little published data are available reporting the safety of chronic or short-term supplemental oxygen in non-surgical patients who have received bleomycin. In 1978, Goldiner et al. published the first report of postanesthetic complications in patients who received bleomycin for germ cell tumours and later underwent retroperitoneal lymph node dissection or resection of pulmonary metastases.[7] Five patients died of rapidly progressive respiratory failure. In a subsequent prospective study of 12 similar patients, the mean FIO2 was reduced to 0.24 from 0.39 and the crystalloid administration was significantly reduced from 5.86 mg/kg/h to 3.87. These patients experienced no postoperative pulmonary complications. Goldiner et al. concluded that the FIO2 during and after surgery should be kept as low as possible and that fluid status should be closely monitored to avoid excessive crystalloid administration.[7] These recommendations for anesthetic management remain the guidelines used by most anesthesiologists today.[12] Several similar case studies have been reported.[8,13] Other investigators attribute the absence of postoperative complications to the administration of a low FIO2 and limited fluids.[14]

Contrary to these recommendations, several more recent publications, which have reviewed over 300 patients undergoing general anesthesia following bleomycin containing regimens for germ cell tumors, have indicated no excess in pulmonary toxicity related to intraoperative or postoperative oxygen therapy.[10,11,15] There has been no substantial change in the anesthetic guidelines for these patients, despite the data obtained from these more recent studies. Several of these investigators have stressed that safe anesthesia for these patients may demand high flow oxygen to avoid risk of intraoperative hypoxia, particularly when one lung anesthesia and ventilation is required for lobectomy.[12,16]

Published data regarding the safety of exposure to high flow oxygen during recreational activities such as scuba diving are limited and patients should be counselled that safety cannot be assured during these activities.

Implementation of this guideline may reduce treatment-related morbidity and mortality. The magnitude of the benefit is expected to be modest given the overall low rate of BPT in current clinical practice. The success of this guideline should be evaluated by careful reporting of treatment-related toxicity in all at risk patients as it is unlikely that prospective clinical trials will be done.

RECOMMENDATIONS

1. The conflicting evidence suggests that caution regarding oxygen therapy be continued, but that patients should not be denied oxygen therapy if hypoxia is documented or anticipated.
2. If supplemental oxygen is required, the lowest FIO_2 that maintains adequate tissue oxygenation (as measured by arterial blood gasses or pulse oximetry) should be provided.
3. Preoperative anesthesia consultation should be mandatory for patients with a history of bleomycin therapy.
4. Recreational use of high flow oxygen (e.g., scuba diving) should be discouraged.
5. Patients should be encouraged to carry wallet cards or wrist bracelets alerting caregivers to possible toxicity associated with oxygen therapy.

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