Drug Monograph

A - Drug Name

bleomycin

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B - Mechanism of Action and Pharmacokinetics

Bleomycin is an antibiotic complex produced by fermentation from Streptomyces verticillus. It causes single- and double-strand DNA breaks through formation of an intermediate iron complex. DNA synthesis, and to a lesser degree, RNA and protein synthesis are inhibited. Bleomycin is cell cycle phase-specific.

Absorption	Oral: no Well absorbed after parenteral (IV, Subcut, IM) administration. About 45% of the dose is absorbed into the circulation after intrapleural administration. Absorption from subcut is delayed and may resemble a slow IV infusion.
Distribution	Rapid distribution to tissues. High concentrations in skin, lung, kidney, peritoneum and lymphatics. Low concentrations are found in the bone marrow. Cross blood brain barrier? no PPB Limited
Metabolism	Inactivated by hydrolases in many tissues. The liver and GI tract show the highest rate of inactivation, while skin, lungs and kidneys show a lower rate.

	Squamous cells are highly sensitive to bleomycin due to their low bleomycin hydrolase content.	
	Active metabolites	yes
	Inactive metabolites	yes
Elimination	Excreted by kidneys; terminal half-life increases exponentially as creatinine clearance falls. Elimination during the first 24 hours is lower after most intracavitary administrations than after IV administration.	
	Urine	66% unchanged
	Half-life	2-5 hours (IV bolus) 5.3 hours (intraperitoneal) 3.4 hours (intrapleural) 9 hours (continuous IV infusion)

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C - Indications and Status

Health Canada Approvals:

- Squamous cell cancer - head and neck, skin, penis, cervix and vulva
- Hodgkin and Non-Hodgkin lymphoma (including lymphosarcoma and reticulum cell sarcoma)
- Testicular cancer
- Malignant pleural effusion

The response is poorer in patients with head and neck cancer who have received previous radiotherapy.

Other Uses:

- Germ Cell Cancers

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D - Adverse Effects

Emetogenic Potential: Minimal

Extravasation Potential: None

ORGAN SITE	SIDE EFFECT* (%)	ONSET**
Cardiovascular	Arterial thromboembolism (rare)	E
	Hypotension (rare)	I
	Other - Pleuropericarditis (rare)	E
	Venous thromboembolism (<10%)	E
Dermatological	Alopecia (30%) (partial)	E
	Nail disorder (11%)	E D
	Other - Hyperkeratosis (≤ 50%; hands, nails)	E D
	Radiation recall reaction (rare)	I
	Rash , pruritis (8%; skin folds, friction areas)	E
	Skin hyperpigmentation (41%) skin folds, nail cuticles, friction areas, IM injection sites	E D
Gastrointestinal	Anorexia, weight loss (29%)	E
	Mucositis (30%)	E
	Nausea, vomiting (15%)	I
General	Fatigue (16%)	E
	Fever, chills (50%) (50% with IV; 25% with IM)	I
	Tumour pain (rare)	E
Hematological	Hemolytic uremic syndrome (rare)	E
Hepatobiliary	↑ LFTs (rare)	E
Hypersensitivity	Anaphylaxis (<10%) (lymphoma patients 1%)	I
Injection site	Phlebitis (rare)	I E
Renal	Creatinine increased (rare)	E
Respiratory	Pneumonitis (10%) (1% fatal)	D
Vascular	Peripheral ischemia (Raynaud's; with vinblastine)	E

* "*Incidence*" may refer to an absolute value or the higher value from a reported range.
"*Rare*" may refer to events with < 1% incidence, reported in post-marketing, phase 1 studies, isolated data or anecdotal reports.

** I = *immediate* (onset in hours to days) E = *early* (days to weeks)
D = *delayed* (weeks to months) L = *late* (months to years)

The most common side effects for bleomycin include fever/chills, skin hyperpigmentation, hyperkeratosis, alopecia (partial), mucositis, anorexia, fatigue, nausea/vomiting, nail disorder, and pneumonitis.

Skin and mucosal changes are the most frequent side effects, occurring in approximately 50% of treated patients and include stomatitis, alopecia, hyperpigmentation, ulceration, erythema, hyperkeratosis, nail changes, rash, vesiculation, tenderness, pruritus, peeling, striae and bleeding. Hypoesthesia may occur at the onset of skin toxicity, and may progress to hyperesthesia. Adverse mucocutaneous effects usually develop in the 2nd or 3rd week of bleomycin treatment. These appear to be dose-related and are usually observed after 150-200 units of bleomycin have been administered. Discontinuation of bleomycin due to these toxicities has occurred in 2% of patients. Bleomycin can cause unusual pigmentation on the trunk consisting of linear streaks with crisscross patterns in 8-22% of patients.

Fever and chills occur in approximately 50% of patients. These reactions usually occur starting a few hours after treatment, and may last up to 4-12 hours. Acetaminophen q3-4h prn can be used to control fever if it occurs. **Anaphylaxis** is reported in 1% of patients with lymphoma after the 1st or 2nd dose; it may be immediate or delayed for several hours.

Bleomycin **lung toxicity** occurs in 10% of patients and is fatal in 1%. Changes in pulmonary functions tests occur in 20% of patients receiving bleomycin. Dyspnea and fine rales are early symptoms of pulmonary toxicity. The clinical symptoms, radiologic and microscopic findings are not specific to bleomycin lung toxicity. The incidence of pulmonary toxicity increases significantly at a cumulative dose of >400 U. Risk factors include age >70 years, pre-existing pulmonary disease, coexisting renal failure, prior or concomitant thoracic radiation therapy, subsequent high-dose oxygen exposure (e.g. during anesthesia), smoking or previous exposure to bleomycin within 6 months. Bolus dosing increases the risk of pulmonary toxicity. It has also been observed occasionally in young patients receiving low doses.

Bleomycin therapy should be withheld if the pulmonary diffusion capacity for carbon monoxide (DLCO) falls to 30-35% of initial value, if the forced vital capacity (FVC) falls significantly, or if there are any clinical or radiographic features indicating pulmonary toxicity. Pneumonitis due to bleomycin should be treated with corticosteroids in an effort to prevent progression to fibrosis. Appropriate antibiotic therapy should be given for infectious pneumonitis. Patients should be warned that uncontrolled oxygen should be avoided except briefly in an emergency and to avoid increased oxygen pressure as in scuba diving.

Bleomycin has the potential to enhance radiation injury to tissues. While often called **radiation recall reactions**, the timing of the radiation may be before, concurrent with or even after the administration of bleomycin. Recurrent injury to a previously radiated site may occur weeks to months following radiation.

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E - Dosing

Refer to protocol by which patient is being treated.

Screen for hepatitis B virus in all cancer patients starting systemic treatment. Refer to the hepatitis B virus screening and management guideline.

Maximum lifetime doses should not exceed 400 units (or 200 units/m^2; less for patients with lung function or renal impairment), due to increased pulmonary toxicity risk. Not to exceed 100 units/m^2 in patients with prior or concurrent lung radiation and in patients over 70 years. For intrapleural administration, consider the absorption in determining the cumulative dose (45% absorbed).

Adults:

Intravenous: 10-20 units/m² (or give IM/SC) Weekly or twice weekly

Intrapleural: 50 to 60 units (not exceeding 1 unit/kg or 40 units/m2 for geriatric patients)

Dosage with Toxicity:

Toxicity Grade / Counts x 10^9/L	**Action / % previous dose**
Pulmonary: Pneumonitis; DL_{CO} ≤ 35% of baseline; Rapid ↓in FVC	Discontinue and investigate. If confirmed treat with corticosteroids.
Cardiac : ECG changes; pleuropericarditis	Hold and investigate; consider ↓ infusion rate or discontinue.
Grade 3 (related organ)	Hold until ≤ grade 2, then 75%
Grade 4 (related organ)	Discontinue

Management of Infusion-related reactions:

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

Grade	Management	Re-challenge
1 or 2	• Stop or slow the infusion rate. • Manage the symptoms. **Restart:** • No specific recommendations can be made at this time.	• No specific recommendations can be made at this time.
3 or 4	• Stop treatment. • Aggressively manage symptoms.	

Dosage with Hepatic Impairment:

No adjustment required.

Dosage with Renal Impairment:

Creatinine clearance (mL/min)	% usual dose
10 – 50	75%
< 10	50%

Children:

Refer to protocols being used.

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F - Administration Guidelines

IM, SC:

- Reconstitute in 1-5mL sterile water or normal saline for injection (concentration 3 to 15 units/mL)

IV:

- Reconstitute with 5-10mL Normal Saline.
- May be given by direct IV push over 10 minutes, followed by a Saline flush, if no IV line has been set up.
- Or may further dilute in 50-100mL Normal Saline (0.3 to 3 units/mL) and infuse over 10-15 minutes.

Intrapleural:

- Dissolve drug in 50 to 100 mL Normal Saline
- Instill via an indwelling thoracostomy tube after drainage. Refer to local guidelines for administration procedures.

- Store unopened vial between 2-8ºC. Do not freeze.

Also refer to the CCO guideline for detailed description of Management of Cancer Medication-Related Infusion Reactions.

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G - Special Precautions

Contraindications:

- Patients who have demonstrated hypersensitivity to the drug or to its excipients

Other Warnings/Precautions:

- Caution should be exercised when used concomitantly with nephrotoxic drugs as they may reduce bleomycin clearance.
- Bleomycin should be used with extreme caution in patients with pre-existing renal or pulmonary disease, and in patients over the age of 70. Patients should avoid high FIO_2 for at least a year after completion (i.e. during anesthesia).

Other Drug Properties:

- Carcinogenicity: Yes

Pregnancy and Lactation:

- Mutagenicity: Yes
- Teratogenicity: Yes
- Pregnancy:
  Bleomycin is not recommended for use in pregnancy. Adequate contraception should be used by patients and their partners during bleomycin treatment and for at least **6 months** after the last dose. (general recommendation)
- Excretion into breast milk: Unknown
  Breastfeeding is not recommended during treatment.
- Fertility effects: Probable
  Bleomycin treatment may cause irreversible infertility.

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H - Interactions

AGENT	EFFECT	MECHANISM	MANAGEMENT
Cisplatin or other nephrotoxins	↓ clearance of bleomycin in patients treated previously or concurrently with cisplatin	cisplatin-induced decrease in GFR	monitor for excessive bleomycin toxicity, especially pulmonary
Drugs that may cause pulmonary toxicity (e.g. BCNU, mitomycin, cyclophosphamide, methotrexate, gemcitabine)	↑ risk of pulmonary toxicity with concurrent bleomycin use	additive	monitor for pulmonary toxicity
digoxin	↓ effect of digoxin	↓ absorption of digoxin	monitor
phenytoin	↓ efficacy of phenytoin	↓ absorption of phenytoin	monitor phenytoin serum levels; adjust phenytoin dose if required.

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I - Recommended Clinical Monitoring

Treating physicians may decide to monitor more or less frequently for individual patients but should always consider recommendations from the product monograph.

Refer to the hepatitis B virus screening and management guideline for monitoring during and after treatment.

Recommended Clinical Monitoring

Monitor Type	Monitor Frequency
Liver function tests (if failure suspected)	Baseline and as clinically indicated
Renal function tests	Baseline and before each cycle
Clinical assessment of mucocutaneous or respiratory effects, infusion-related reactions, thromboembolism	At each visit; continue to monitor for pulmonary toxicity for approximately 2 months after treatment completion

Grade toxicity using the current NCI-CTCAE (Common Terminology Criteria for Adverse Events) version

Suggested Clinical Monitoring

Monitor Type	Monitor Frequency
Pulmonary tests, including DL_{CO}, if patient has pre-existing pulmonary dysfunction, or has had prior pulmonary radiation, if age >70, or if total cumulative Bleomycin dose >400 mg	Baseline, regular (i.e. monthly) and as clinically indicated

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K - References

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November 2024 Updated Pregnancy and Lactation section

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L - Disclaimer

Refer to the New Drug Funding Program or Ontario Public Drug Programs websites for the most up-to-date public funding information.

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