INJECTION

BLEOCIN 15000 IU

(Bleomycin Sulfate) B.P

Antineoplastic Agent

انجکشن

بلیوسین

(بلیومائی سین سلفیٹ) بی پی

اینٹی نیو پلاسٹک ایجنٹ

Action and Clinical Pharmacology : Experiments with isolated DNA have shown that bleomycin binds to the DNA molecule and cleaves it. This results in the inhibition of DNA synthesis. There is also evidence of lesser inhibition RNA and protein synthesis. The activity of bleomycin seems to be cell phase specific. Cyclic and continuous administration of bleomycin has been shown to be more effective than bolus dosing in in-vivo systems. Bleomycin is well absorbed after parenteral, (i.v., s.c., i.m. and intrapleural) but not after oral administration. Tissue distribution was evaluated in mice and was found to be high in skin, kidney, lung, peritoneum, lymphatics and solid tumor and tumor cells in ascites. Bleomycin does not cross the blood-brain barrier. Several tissues have demonstrated a capacity to degrade bleomycin. The liver and gastrointestinal tract show the highest rate of inactivation. The skin, lungs and kidney show a lower rate which may account for the site-specific toxicity of the drug. Bleomycin half-life varies with creatinine clearance and is of 2 to 5 hours after i.v. administration to patient with normal kidney function. With continuous i.v. infusion, the terminal half-life of bleomycin is 9 hours for adults and about 2.3 hours for children. In children less than 3 years of age, the terminal half-life of bleomycin administered by rapid i.v. injection is 3 hours.

Pharmacokineties : Patients with Impaired Renal Function: The serum half-life of bleomycin is markedly prolonged in patients with renal dysfunction. The bleomycin half-life increases as the creatinine clearance decreases.

Indications And Clinical Uses : Bleomycin should be used as first line therapy and/or adjuvant to surgery and radiation therapy. It has been shown to be useful in the following neoplasma: Squamous Cell Carcinoma: skin, larynx and paralarynx, penis, cervix,vulva. Bleomycin in combination with radiotherapy shows improved results in lung cancer cervical carcinoma.

Lymphomas : Hodgkin's lymphoma ad non-Hodgkin's lymphoma including reticulum cell sarcoma, and lymphosarcoma.

Other : Bleomycin has been shown to produce responses in some renal carcinomas and soft tissue sarcomas.

Contra-Indications : Patients who have demostrated a hypersensitive or an idiosyncratic reaction to the drug. When used as indicated the physician must weigh carefully the therapeutic benefit versus risk of toxicity which may occur.

Warnings in Clinical States : Idiosyncratic reactions similar to anaphylaxis have been reported in 1% of lymphoma patients treated with bleomycin. Since these usually occur after the first or second dose, careful monitoring is essential after these doses. It is recommended that bleomycin be administered under the supervision of a qualified physician experienced in the use of cancer chemotherapeutic agents. Since facilities for necessary laboratory studies must be available , hospitalization of patients is recommended. Patients receiving bleomycin must be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function. Patients who are undergoing bleomycin treatment are predisposed to respiratory failure following exposure to high concentrations of O2 (general anesthesia). Since this effect may be observed for up to 1 year after treatment with bleomycin, the oxygen administration to these patients should be kept at the lowest possible concetrations in order to minimize the risk of severe pneumonitis. Pulmonary toxicities occur in approximately 10% of treated patients. In appproximately 1% , the nonspecific pneumonitis induced by bleomycin progresses to pulmonary fibrosis and death. Although this is age and dose related, the toxicity is unpredictable. A method suggested to lower the incidence of pulmonary toxicity is the continuous i.v. adminstration of bleomycin. Renal or hepatic toxicity, beginning as a deterioration in renal or liver function tests, have been reported, infrequently. These toxicities may occur, however, at any time after irritation of therapy.

Pregnancy : Safe use of bleomycin in pregnant women has not been established.

Precautions : General : Bleomycin should be administered preferably to patients who are hospitalized and who can be observed carefully and frequently during and after therapy. It should be used with extreme caution in patients with significant impairment of renal function or compromised pulmonary function due to disease other than malignancy, and in patients over 70 years of age because of the apparent increased danger of pulmonary toxicity. Frequent roentgenograms are not a preferable method of follow-up or detection of pulmonary toxicity from bleomycin. Current practice of frequent physical examination (cough, basal rales and pleuritic chest pain are frequently first signs of toxicity) and baseline evaluation of carbon monoxide diffusion capacity which also allows for the exclusion of patients with low pulmonary reserve, as well as for follow-up of progression of the pneumonitis after cessation of bleomycin therapy. If pulmonary changes are noted, treatment should be discontinued until it can be determined whether the cause is drug related. Pneumonitis due to bleomycin should be treated with corticosteroids in an effort to prevent progression to pulmonary fibroses. Infectious pneumonitis should receive appropriate antibiotic therapy.

Adverse Reactions : Skin : 50% of the patients develop either hyperpigmentation of the skin, hyperkeratosis of hands and nails and edema and erythema of the hands and feet. The skin toxicity occured more frequently at higher doses: 200 to 300 unit range and can be dose limiting. Rash forms on the pressure areas of the body and abdominal skin areas. It is a common side effect (due to accumulation of the bleomycin in the skin) and is reported to occur in 8% of treated patients within a few days to 2 to 3 weeks at doses of 187.5 IU to 5250 IU/m.

Pulmonary : Pulmonary toxicity is potentially the most serious side effect, occurring in approximately 10% of treated patients. The most frequent menifestation is pneumonitis occasionally progressing to pulmonary fibrosis which may result in death. Approximately 1% of patients treated succumb to pulmonary toxicity. Pulmonary toxicity is usually both dose and age related, being more common in patients over 70 years of age receiving over 400,000 IU units total dose; however, this toxicity is unpredictable and has been seen occasionally in young patients receiving low doses. This identification of patients with pulmonary toxicity due to bleomycin has been extremely difficult, due to the lack of specificity of the clinical syndrome, the x-ray changes and even the tissue changes seen on examination of biopsy and autopsy speciments. Bleomycin induced pneumonitis apparently produces dyspnea and fine rales that are in no way different from those produced by infectious pneumonias, or the signs and symptpoms produced by primary or metastatic lung disease in some patients. If pulmonary changes are noted, treatment should be discontinued until it can be determined if they are drug related. Sequential measurement of the pulmonary diffusion capacity for carbonmonoxide (DLCO) during treatment with bleomycin may be an indicator of subclinical pulmonary toxicity. It is recommended that the DLCO be monitored monthly if it is to be employed to detect pulmonary toxicities, and thus the drug should be discontinued when the DLCO falls below 30 to 35% of the pretreatment value. Concurrent or prior lung, irradiation will also predispose patients to increased pulmonary toxicity. The reaction which may be immediate or after several hours delay occurs only after the first or second dose. It consists of hypo-tension, fever, chills, mental confusion and wheezing. in order to minimize the incidence of pneumonitis due to bleomycin therapy, it is recommeded not to exceed total dose 20000 not to exceed 100,000 IU concurrent lung irradiation is also given, not to exceed 100 units/min patients over the age of 70 and to use continuous infusion to avoid peak serum levels.

Fever : Pretreatment with antipyretics or antihistamines is frequently given as fever occurs in 50% of patients with i.v. administration and 25% with i.m. administration.

Gastrointestinal Toxicity : Mucositis and stomatitis occur in 30% of patients.

Other : Fever, chills and vomiting are frequently reported side effects. Anorexia and weight loss are common and may persist long after termination of this medication. Pain at tumor site, phlebitis, and other local reactions are reported in frequently. There are also isolated reports of Raynaud's phenomenon occurring in patients with testicular carcinomas treated with a combination of bleomycin and vinblastine. It is currently unknown if the cause for the Raynaud's phenomenon in these cases is the disease, either drug, or a combination of any or all of these. Toxicity to the renal, hepatic and CNS is rare, but as with any potent drug, these symptoms should be monitored. It is noteworthy that there has been little evidence of bone marrow or immunological depression to date, This is contrary to the currently available antineoplastic drugs.

Dosage and Administration : All lymphoma patients should be started with 2000 IU units or less for the first 2 doses. If no acute reaction occurs, then the regular dose schedule may be followed. Bleomycin may be given by the i.m., i.v, intra-arterial, intracavitary or s.c. routes.

The following dose schedule is recommended : Squamous Cell Carcinoma, Lymphosarcoma, Reticulum Cell Sarcoma

Testicular Carcinoma : 250 to 500 IU/kg (10000 to 20000 IU/m given i.v. or i.m. weekly or twice weekly.

Hodgkins's Disease : 250 to 500 IU/kg. After a 50% response, a maintenance dose of 1 unit daily s.c. or 50000 IU weekly i.v. or i.m. should be given . Toxicity of bleomycin appears to be dose related with a striking increase when the total dose is over 400000 IU. Total doses over 400000 IU should be given with great caution. Hodgkin's and testicular improvement are prompt and noted within 2 weeks. If no improvement is seen by this time, chances of improvement are very low. Squamous cell cancers respond more slowly, slowly, sometimes requiring as long as 3 weeks before improvement is noted.

Impaired Renal Function : For patients with impaired renal function, the following dosage schedule is recommended.

Patients with Moderate Renal Failure (GFR 10-50mL/min) : Reduce to 75% of normal dose at the normal dosage interval.

Patients with Severe Renal Failure (GFR <10mL/min) : Reduce to 50% of normal dose at the normal interval.

Patients with GFR greater than 50mL/min : No dosage adjustment is required. I.V. or Intra-arterial : Dissolve the contents of the vial in 5 to 10 mL of either Sterile Water for Injection of 0.9% Sodium Chloride Injection.

Precaution for Handling : Reconstituted solutions may be stored at room temperature for 24 hours or refrigerated at 2 to 8°C for up to 48 hours. Unused portions should be discarded after that time.

Warning : As with all parenteral drug products, i.v. admixtures should be inspected visually for clarity, particulate matter, precipitate discoloration and leakage prior to administration, whenever solution and container permit. Solutions showing haziness, particulate matter, precipitated, discoloration or leakage should not be used.

Handling & Disposal :

1) Preparation of cytotoxic agents such as bleomycin should be done in a vertical laminar flow hood. 2) Personnel preparing cytotoxic agents should wear PVC gloves, safety glasses, disposable gowns and masks. 3) All needles, syringes, vials and other materials which have come in contact with bleomycin should be segregated and incinerated at 1000°C or more. Sealed containers may explode. 4) Personnel regularly involved in the preparation and handling of cytotoxic agents should have biannual blood examinations.

Instrusctions :

Store at 2-8°C. Protect from heat light and moisture as melting of drug may occurs.

Keep all medicines out of the reach of children.

To be sold on prescription only.

Note : Use immediately after reconsititution.

Availability :

Bleocin Injection. Each vial contains: Bleomycin Sulfate B.P. 15000IU.

خوراک: ڈاکٹر کی ہدایات کے مطابق استعمال کریں۔

ہدایات: 2 سے 8 ڈگری سینٹی گریڈ درجہ حرارت پر رکھیں۔

گرمی روشنی اور نمی سے بچائیں ورنہ دوائی پگھل سکتی ہے۔

تمام دوائیں بچوں کی پہنچ سے دور رکھیں۔

صرف مُستند ڈاکٹر کے نسخے پر فروخت کریں۔

Manufactured by :

PHARMEDIC LABORATORIES (PVT) LIMITED.

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