

A Fatal Hyperpyrexial Response to Bleomycin Following Prior Therapy: A Case Report and Literature Review

FRED ROSENFELT, M.D., JOHN PALMER, M.D.,
IRWIN WEINSTEIN, M.D., AND BARRY ROSENBLOOM, M.D.

Cedars-Sinai Medical Center, Department of Oncology, Los Angeles, California

Received August 16, 1982

Bleomycin is an effective drug used in the therapy of many malignant diseases. Such toxicities as fever, chills, and pulmonary fibrosis are well known to occur following administration of this drug. A rare fatal hyperpyrexial response has also been noted with this agent. We describe a case of fatal hyperthermia after an injection of bleomycin. Unlike earlier reported cases, our patient developed her reaction following prior uneventful therapy with bleomycin rather than as a response to initial treatment. Factors that may be related to the hyperpyrexial response to bleomycin are discussed and the relevant literature reviewed.

Bleomycin is an effective anti-tumor agent often used in the therapy of testicular carcinoma, lymphoma, and lung cancer. Several toxic reactions have been reported with this drug, including fever, chills, nausea, vomiting, and pulmonary fibrosis. An uncommon fatal hyperpyrexial response to this agent has also been observed [4,6,7,8]. This fulminant hyperthermia reaction has usually been noted following the initial administration of bleomycin. We report an unusual case of this hyperpyrexial response in a lymphoma patient treated with bleomycin several weeks after prior administration of this drug.

CASE REPORT

A 50-year-old white female was evaluated for fevers, sweats, and lymphadenopathy. A cervical lymph node biopsy revealed a diffuse histiocytic lymphoma. Staging with a CAT scan, gallium scan, and bone marrow biopsy was consistent with Stage IIIB disease. The patient was treated with cyclophosphamide, doxorubicin, vincristine, and prednisone (CHOP) with significant improvement. Prior to the next course of chemotherapy the patient experienced fevers, sweats, and adenopathy. Therapy was initiated with bleomycin and vincristine because of persisting neutropenia. The patient received a test dose of bleomycin subcutaneously without reaction. Subsequently, she received 9 mg of bleomycin intravenously and experienced chills and fever two hours later. The patient responded to therapy with acetaminophen and Benadryl. The patient's symptoms resolved and she was subsequently treated with CHOP and discharged.

A week later, the patient again developed fever and chills. Her leucocyte count was 800 with 10 percent neutrophils. Cultures were obtained and antibiotics given. All cultures were negative at four days and she remained febrile despite antibiotic

therapy. For this reason, bleomycin and vincristine were again administered. Prior to her bleomycin injection, the patient was pre-treated with Benadryl and acetaminophen. Two hours following her bleomycin therapy, the patient developed severe rigors, a temperature of 107.5° rectally, and rapidly lost consciousness. On examination, she was noted to be hypotensive, tachycardic, and tachypneic. Following intubation, the patient received externally applied ice packs, saline, Benadryl, epinephrine, Solumedrol, and acetaminophen with normalization of her temperature within two hours. After her initial resuscitation, the patient developed disseminated intravascular coagulation, renal failure, hepatic failure, and cardiovascular collapse. Despite intensive therapy with antibiotics, heparin, steroids, transfusions, and hemodynamic support, the patient died within 48 hours. All subsequent cultures were negative. Permission for a postmortem examination was refused.

DISCUSSION

Fever following bleomycin therapy is relatively common, occurring in approximately 20–53 percent of patients [1,2,3]. This febrile reaction may be less frequent with lower doses of drug and tends to abate with subsequent treatment [1,4]. The onset of fever is usually within two to six hours of drug administration and is often associated with chills. The patient's temperature may remain elevated for several hours [1]. The role of therapy in preventing this toxicity has not been proven.

The mechanism of bleomycin hyperpyrexia in man is uncertain. Initially, it was thought to be a consequence of endotoxin contamination of bleomycin preparations. Dinarello et al. [5], however, demonstrated that the febrile reaction due to bleomycin appeared unrelated to contaminating bacterial endotoxin. Rather, they proposed that the drug results in the release of an endogenous pyrogen. The exact source and action of this pyrogen remain unknown.

A number of cases of fulminant hyperthermia have been reported. Blum et al. [4] observed four deaths and six sublethal reactions in 808 patients receiving this drug. They noted that 6 percent of lymphoma patients experienced this response. Levy [6] Ma [7], and Durbin [8] have described extreme hyperpyrexial responses occurring in patients receiving 7.5 mg, 6 mg, and 1 mg of bleomycin as test doses. The clinical picture observed with bleomycin-induced hyperthermia in many reports is similar to that of our patient. In most cases, several hours after bleomycin therapy high fevers, hypotension, and cardiopulmonary collapse occur. Despite intensive therapy and hemodynamic support most patients die.

In many of the previously reported cases, this hyperthermic response was noted as occurring with the initial injection of the drug. In our case, the reaction occurred following prior therapy with bleomycin. Moreover, these injections were several weeks apart with the usual toxic reactions noted following the first treatment. In addition, prior to her fatal response, this patient was pre-treated with acetaminophen and Benadryl. Our patient did receive intravenous bleomycin. Mosher et al. [3] have reported a decreased frequency of toxicity with intra-muscular as compared to intravenous injections of bleomycin. Whether the route of administration is of significance in the development of this fulminant hyperthermic response is difficult to ascertain.

It is of interest to speculate upon the possible role of endogenous pyrogen as a mediator of this reaction. Conceivably, tumor lysis and release of pyrogens may be responsible for the initiation of this reaction. Of importance in this regard may be lymphomas or tumors associated with fever in which endogenous pyrogens may play a role. Although rare, perhaps such patients should be monitored closely for

bleomycin-induced hyperthermia. The role of steroids, Benadryl, and antipyretics in preventing this problem is uncertain, although they should be considered as pre-treatment in such cases.

ACKNOWLEDGEMENT

The authors acknowledge the aid of Roberta Cornwall in the preparation of this manuscript.

REFERENCES

1. Yagoda A, Murherji B, Young C, et al: Bleomycin, an antitumor antibiotic. *Ann Int Med* 77:861-870, 1972
2. Rudders RA: Treatment of advanced lymphomas with bleomycin. *Blood* 40:317-332, 1972
3. Mosher MB, DeConti RC, Bertino JR: Bleomycin therapy in advanced Hodgkin's disease and epidermoid cancers. *Cancer* 30:56-60, 1972
4. Blum RH, Carter SK, Agre K: A clinical review of bleomycin—A new antineoplastic agent. *Cancer* 31:903-914, 1973
5. Dinarello CA, Ward SB, Wolff SM: Pyrogenic properties of bleomycin. *Cancer Chemo Reports* 57:393-398, 1983
6. Levy RL, Chiarillo S: Hyperexia, allergic-type response and death occurring with low-dose bleomycin administration. *Oncology* 37:316-317, 1980
7. Ma DDF, Isbister JP: Cytotoxic-reduced fulminant hyperexia. *Cancer* 45:2249-2251, 1980
8. Durkin WJ, Pugh RP, Solomon J, et al: Treatment of advanced lymphomas with bleomycin. *Oncology* 33:140-145, 1976
9. Bennett JM, Reich SD: Bleomycin diagnosis and treatment drugs five years later. *Ann Int Med* 90:945-948, 1979
10. Oken MM, Lach J: Corticosteroid and antihistamine modification of bleomycin-induced fever. *Proc Soc Exp Biol Med* 161:594-596, 1979