The HKU Scholars Hub The University of Hong Kong 香港大學學術庫

Title	Fulminant hyperpyrexia induced by bleomycin
Author(s)	Leung, WH; Lau, JY; Chan, TK; Kumana, CR
Citation	Postgraduate Medical Journal, 1989, v. 65 n. 764, p. 417-419
Issued Date	1989
URL	http://hdl.handle.net/10722/44985
Rights	Creative Commons: Attribution 3.0 Hong Kong License

Postgraduate Medical Journal (1989) **65**, 417 – 419

Fulminant hyperpyrexia induced by bleomycin

Wing-Hung Leung, Johnson Y.N. Lau, Tai-Kwong Chan and Cyrus R. Kumana

Department of Medicine, University of Hong Kong, Queen Mary Hospital, Pokfulam Road, Hong Kong.

Summary: Mild and self-limiting fever following bleomycin use is common, and a fatal hyperpyrexial response occurs rarely. In previously reported cases, such hyperpyrexia occurred either after the initial administration of the drug or during subsequent therapy following an initial pyrexial response. We describe a fatal hyperpyrexial reaction after bleomycin in a patient with T-cell lymphoma who had had no febrile response when she received her initial injection 3 weeks earlier. Since the occurrence of this hyperpyrexial response is unpredictable, health care workers as well as patients and relatives should always be alert to this potentially lethal complication and prompt measures should be taken in any patient who develops fever after bleomycin use.

Introduction

Bleomycin, the generic name for an antibiotic isolated from *Streptomyces verticillus*, is now used frequently as an anti-cancer drug against a wide variety of tumours including lymphoma, testicular tumours and squamous cell carcinoma.[1] Although fever following bleomycin therapy occurs commonly, it is usually mild and self-limiting.[1,2] Rarely, bleomycin can induce a fulminant hyperpyrexia associated with a high mortality.[1,3–6] In previously reported fatal cases, such hyperpyrexia either follows the initial administration of the drug or during subsequent therapy following an initial mild and self-limiting febrile response. We report a unique case of fatal bleomycin-induced hyperpyrexia in a T-cell lymphoma patient, who had received a prior initial injection of bleomycin 3 weeks earlier without a febrile response.

Case report

A 42 year old Chinese female teacher presented with marked constitutional symptoms consisting of malaise, night sweats, anorexia, profound weight loss and hepato-splenomegaly for 3 weeks. Investigations showed pancytopenia and bone marrow examination revealed reactive changes with small epithelioid granuloma and reactive haemophagocytosis. The patient subsequently underwent a laparotomy which revealed enlarged para-aortic, mesenteric and iliac lymph nodes in addition to the hepato-splenomegaly. Splenectomy, wedged liver biopsy and multiple lymph nodes sampling were performed. Isoflurane and nitrous oxide were used as inhalational anaesthetic agents. Vecuronium was used as the muscle relaxant.

Correspondence: Wing-Hung Leung, M.B., M.R.C.P.
Accepted: 23 January 1989

Histology showed peripheral T-cell lymphoma of the pleomorphic type. Postoperatively whilst still an inpatient, she was treated with a chemotherapeutic combination at half the conventional dosage, which initially consisted of bleomycin, 3 mg i.v.; doxorubicin, 30 mg i.v.; cyclophosphamide, 400 mg i.v.; vincristine, 1 mg i.v.; dexamethasone, 4 mg orally for 5 days; and methrotrexate, 140 mg i.v. on day 8 and day 15 followed by oral folinic acid rescue (m-BACOD). There was no reaction to the first course of chemotherapy and her presenting constitutional symptoms subsided after the treatment.

Three weeks later, a second course of chemotherapy with increased dosage was given (bleomycin 6 mg; doxorubicin 45 mg; cyclophosphamide 600 mg; vincristine 2 mg) in the outpatient clinic. Three hours after the injection, she developed severe rigors and profuse sweating. One hour later, she was admitted to hospital, whereupon she spiked a temperature in excess of 42°C rectally (i.e. beyond the upper range of the scale). She was delirious and unresponsive to commands with generalized muscle rigidity. Her blood pressure was 70/40 mmHg with a pulse rate 160/min. Arterial blood gases revealed a metabolic acidosis with pH 7.25 and bicarbonate 12 mmol/l. She was treated with intravenous fluid, sodium bicarbonate, chlorpromazine, methylprednisolone 1 g, indomethacin suppository as well as externally applied ice packs and cold water sponging. She developed one episode of generalized tonic-clonic seizure which was controlled with intravenous diazepam. She lapsed rapidly to respiratory arrest which necessitated intubation and mechanical ventilation. About 2 hours after admission, her temperature had dropped to 34.7°C. There was also clinical and laboratory evidence of disseminated intravascular coagulation. Fresh frozen plasma and platelet concentrates were administered

© The Fellowship of Postgraduate Medicine, 1989

and the generalized bleeding was controlled. However, she remained unconscious with dilated and unresponsive pupils, generalized flaccidity and anuria. Despite intravenous dopamine and adrenaline, the hypotension persisted and she died 8 hours later. Microbiological cultures of blood, urine and sputum were sterile. Permission for autopsy was refused.

Discussion

Among the various side effects of bleomycin, fever is common, occurring in 20–60% of patients.[1,2] The fever usually occurs 1 to 4 hours after the initial dose, subsides spontaneously within about 8 hours, and does not necessarily recur with subsequent treatment.[1] More rarely, there is an acute hyperpyrexial reaction with fever $>40°C$, severe chills, rigors, diaphoresis, wheezing, mental confusion, marked hypotension, and anuria.[7]

There are at least 8 reports of fatal fulminant hyperpyrexial reactions. Blum[1] first reported 4 deaths, all were lymphoma patients who had received a first dose of bleomycin (25–40 mg/m^2). Levy[3] and Ma[4] also described similar first dose reactions in 2 patients receiving 7.5 mg and 5 mg of bleomycin respectively. However, bleomycin-induced severe hyperpyrexia can also occur in patients who have received previous therapy of bleomycin. Rosenfelt[5] reported a lymphoma patient who developed the fatal reaction after the second dose of bleomycin (9 mg). Carter[6] described a case of fulminant hyperpyrexia and death in a patient with lymphoma who had previously received 10 full doses of bleomycin, totalling more than 60 mg. In these two reports, a febrile response was also observed after the initial course of treatment. In our case, there was no initial febrile reaction. As observed in the previous reports,[4–6] disseminated intravascular coagulation (DIC) was also present in our patient. This is probably due to the endothelial and blood cell damage induced by hyperpyrexia *per se*, since DIC is also well documented with anaesthetic-induced malignant hyperpyrexia and heat stroke.[8,9]

The mechanism of these hyperpyrexial responses is uncertain. They are not consistent with classical anaphylaxis. Significantly, our patient had undergone uneventful general anaesthesia, which would suggest that the hyperthermia was produced by a different mechanism from that due to anaesthetic agents. Dinarello[10] has demonstrated in rabbits that intravenous bleomycin causes release of a circulating endogenous pyrogen. Moreover incubation of both human and rabbit white cells with bleomycin can also release this pyrogen. The observation that bleomycin-induced hyperpyrexia occurs almost exclusively in lymphoma patients suggests that there may be an undue subsceptibility of lymphomatous tissues such that they release endogenous pyrogens following bleomycin therapy. However, the nature of this pyrogen and its mechanism of action is unknown. One possible endogenous pyrogen is tumour necrosis factor which has been shown to produce fever, both through a direct effect on hypothalamic neurones and through the peripheral induction of interleukin-1, as well as shock, disseminated intravascular coagulation and multi-organ damage.[11]

Bleomycin-induced hyperpyrexia has a high mortality. However, prevention is difficult since the reaction is unpredictable. According to anecdotal accounts, pretreatment with antipyretics and antihistamines tends to lessen these febrile reactions.[1] Carter[6] suggested that patients already febrile should not be given bleomycin until the fever is suppressed, since their margin for tolerating additional fever was significantly diminished. Some have recommended that a 1 mg test dose of bleomycin be initially administered to any patient, especially those with lymphoma, for whom bleomycin treatment is contemplated.[1] Since this fatal reaction can occur in patients who have already had prior therapy without reaction, the recommendation for test dose has to be for both the initial and subsequent doses.

Fortunately, this fatal hyperpyrexial reaction is rare. We recommend that physicians and nurses as well as patients and their relatives should be alert to this potential fatal complication. Any patient who has received bleomycin should be closely monitored. The occurrence of any pyrexia after bleomycin therapy should prompt one to take emergency measures for rapid cooling. Treatment for established cases is mainly supportive, the role of antipyretics, diphenhydramine, corticosteroid and chlorpromazine is still uncertain.

References

1. Blum, R.H., Carter, D.K. & Agre, K. A clinical review of bleomycin – a new antineoplastic agent. *Cancer* 1973, **31:** 903–914.
2. Crooke, S.T. & Bradner, W.T. Bleomycin: a review. *J Med* 1976, **7:** 333–428.
3. Levy, R.L. & Chiarillo, S. Hyperpyrexia, allergic-type response and death occurring with low-dose bleomycin administration. *Oncology* 1980, **37:** 316–317.
4. Ma, D.D.F. & Isbister, J.P. Cytotoxic induced fulminant hyperpyrexia. *Cancer* 1980, **45:** 2249–2251.

5. Rosenfelt, F., Palmer, J., Weinstein, I. & Rosenbloom, B. A fatal hyperpyrexial response to bleomycin following prior therapy: A case report and literature review. *Yale J Biol Med* 1982, **55:** 529–531.
6. Carter, J.J., McLaughlin, M.L. & Bern, M.M. Bleomycin-induced fatal hyperpyrexia. *Am J Med* 1983, **74:** 523–525.
7. Mosher, M.B., DeConti, R.C. & Bertino, J.R. Bleomycin therapy in advanced Hodgkin's disease and epidermoid cancers. *Cancer* 1972, **30:** 56–60.
8. Britt, B.A. Malignant hyperthermia. *Clin Anaesth* 1975, **61:** 61–74.
9. Owen, C.A., Bowie, E.J.W. & Thompson, J.H. Jr. In: *The Diagnosis of Bleeding Disorders*, 2nd ed. Little, Brown and Company, Boston, 1975, p. 301.
10. Dinarello, C.A., Ward, S.B. & Wolff, S.M. Pyrogenic properties of bleomycin (NSC-125006). *Cancer Chemother Rep* 1973, **57:** 393–398.
11. Beutler, B. & Cerami, A. Cachectin: more than a tumour necrosis factor. *N Engl J Med* 1987, **316:** 379–385.