Bleomycin-induced Death Following ABVD Chemotherapy for Hodgkin's Disease with Pulmonary Tuberculosis

WANG Huaichong[1], YANG Wei[2], XU Xiaofeng[2*], XU Yingying[1], ZHANG Xuejin[2](*1.Department of Clinic Pharmacy, Integrated Chinese and Western Medicine Hospital of Zhejiang Province, Hangzhou 310003, China; 2.Department of Oncology and Hematology, Integrated Chinese and Western Medicine Hospital of Zhejiang Province, Hangzhou 310003, China*)
WANG Huaichong and YANG Wei contributed equally to this work.

ABSTRACT: OBJECTIVE Bleomycin (BLM) in ABVD regimen has a low therapeutic index. BLM-induced Death which we reported suggested that we should be cautious to use it. **METHODS** It was reported a 74-year-old Chinese man admitted to our hospital for fever, cough was diagnosed with classical Hodgkin's disease with pulmonary tuberculosis. Doxorubicin, 35mg i.v., vinblastine, 4 mg i.v., dacarbazine 500 mg i.v., and BLM 15 mg i.v. were injected on the first day. **RESULTS** Twenty minutes after the BLM injection, the patient spiked a temperature to 41.0 ℃ with concomitant symptoms of dyspnea, hyperhidrosis and coma, and blood pressure dropped to 108/58 mmHg. The patient finally succumbed to multiple organ failure caused by BLM-induced toxicity. **CONCLISION** Chemotherapy regimen including BLM should be cautiously selected for the patients, especially patients >70 years old with pulmonary complication. It should be recommended that the empirical 1 unit test dose is administered after prophylactic agents. If no acute reaction occurs, recommended dosage regimen may then be administered.
KEY WORDS: Hodgkin's disease; pulmonary tuberculosis; bleomycin; death; adverse reation
中图分类号：R969.4　　文献标志码：A　　文章编号：1007-7693(2014)05-0620-04
DOI: 10.13748/j.cnki.issn1007-7693.2014.05.028

采用含博来霉素 ABVD 方案治疗霍奇金淋巴瘤合并肺结核致患者死亡 1 例

王怀冲[1]，杨威[2]，许晓峰[2*]，徐颖颖[1]，张学进[2](1.浙江省中西医结合医院临床药学室，杭州 310003；2.浙江省中西医结合医院肿瘤血液科，杭州 310003)

摘要：目的 ABVD 化疗方案中博来霉素治疗指数较低，本文报道 1 例死亡病例供临床参考，旨在提示临床谨慎应用。**方法** 报道 1 名 74 岁的中国男性患者因发热、咳嗽入院，经诊断为经典霍奇金淋巴瘤合并肺结核。采用 ABVD 化疗方案，第 1 天给予多柔比星 35 mg，长春地辛 4 mg，达卡巴嗪 500 mg，博来霉素 15 mg。**结果** 患者给予博来霉素 20 min 后，体温突然升至 41 ℃并伴有呼吸困难、多汗、昏迷症状，血压下降至 108/58 mmHg，患者最后死于多器官功能衰竭。**结论** 对于合并肺结核的老年霍奇金病患者特别是年龄>70 岁者，应该谨慎选择含有博来霉素的化疗方案。并且在充分给予预防用药后，首先使用 1 mg 的博来霉素进行预实验，如果没有不良反应发生才能全剂量给药。
关键词：霍奇金淋巴瘤；肺结核；博来霉素；死亡；不良反应

Coexistence of Hodgkin's disease(HD) and tuberculosis has been long recognized and is speculated to occur due to the underlying primary immune dysfunction or as a result of immune dysfunction acquired secondary to therapy[1]. Older patients with HD account for approximately 20% of all HD patients. ABVD chemotherapy is regarded as standard of care for these patients with advanced stage HD although escalated BEACOPP has improved survival in one randomized controlled trial[2-3]. Twenty-four percent of older HD patients (aged ≥ 60 years) developed BLM lung toxicity, which occurred with ABVD 91%. Further, the mortality rate that correlated with BLM lung toxicity was 18%[4].

BLM is well known by its antitumor activity

作者简介：王怀冲，男，主管药师　Tel: (0571)56109872　E-mail: whc208@qq.com　杨威为并列第一作者　*通信作者：许晓峰，男，硕士，副主任医师　Tel: (0571)56109811　E-mail: hhxuxiaofeng@126.com

both *in vitro* and *in vivo*. However, adverse reactions that occurred with BLM are very common, and pulmonary toxicity is most serious, which has been considered the dose limiting toxicity of the drug. The lung toxicity of BLM was evidenced by decrease in the body weight, increase in the lung/body weight ratio, and decrease in the response of pulmonary arterial rings to 5-hydroxytryptamine and increase in the contractility of tracheal smooth muscles induced by acetylcholine. Other prominent toxicities include skin rashes, hypotension, pyrexia, chills, coma and vomiting. Test doses of 1 unit or lower should be routinely used to hopefully select out those patients who are susceptible to this life-threatening response[5]. Premedication with antipyretics and antihistamines may prevent or mitigate the responses, for instance, acetaminophen has efficacy as a preventive medication for hyperpyrexia[6]. We report here a case of stage Ⅳ HD in association with pulmonary tuberculosis. Hyperpyrexia, coma, vomiting, and wheezing were caused by BLM following ABVD chemotherapy, and finally all rescue measures failed. Prominent clinical manifestations of this case were presented with special emphasis on his blood pressure and Fi O_2 concentration remaining normal early in the course of BLM intoxication.

1 Case report

A 74-year-old Chinese man presented with a 1-month history of fever and cough associated with right cervical lymph node enlargement (2 cm) with no other symptoms. B-ultrasound examination showed lymph node enlargement bilaterally in the neck and inguen as well as in the left axillary and posterior peritoneum. There were no other abnormalities on physical examination. Thorax computed tomographic scan showed multiple spotty shadows in both of upper pulmonary regions and mediastinal lymphadenopathy. Sputum culture failed to show tuberculosis infection. Diagnosis of tuberculosis was suspected by the enzyme-linked immunospot assay for interferon-γ. Then he accepted diagnostic antituberculotic treatment protocol with isoniazid, rifampin, ethambutol and pyrazinamide. Two weeks later fever and cough disappeared. Immunohistochemical examination of the right cervical lymph node biopsy showed classical HD. The detection of lymph node tissue fusion gene was found with IgH rearranged gene. Bone marrow examination revealed lymphomatous infiltration. He was staged as Ann Arbor ⅣB and planed to undergo 6 cycles of ABVD after two months treatment of antituberculosis drugs.

Doxorubicin, 35 mg i.v., vinblastine, 4 mg i.v., dacarbazine 500 mg i.v., and BLM 15 mg i.v. were successively injected on the first day. Twenty minutes after the BLM injection, he spiked a temperature to 41.0 ℃ with concomitant symptoms of dyspnea, hyperhidrosis and coma, and blood pressure dropped to 108/58 mmHg(126/64 on admission). Simultaneously, heart rate increased to $137 \cdot min^{-1}$. Over the next 3 h, the acute symptoms had been controlled with intravenous methylprednisolone, promethazine by intramuscular injection, mask oxygen-inspiration, alcohol baths, cooling blanket, and his temperature decreased to 38.3 ℃. Despite sustaining febrile and oliguric, he revived 6 h later. However, 4 h later, he suddenly produced hyperspasmia and lockjaw repeatedly, which had relieved after muscle injection of valium, but his blood pressure and Fi O_2 concentration remained normal at that time. Two hours later, blood pressure dropped quickly to 60/30 mmHg and blood oxygen saturation(52%) significantly decreased. Although vigorous therapeutic measures were carried out, it failed.

Before expiring, his leukocytes were markedly raised from $5.6 \times 10^9 \cdot L^{-1}$ to $23.8 \times 10^9 \cdot L^{-1}$ due to acute tumor lysis syndrome, without bacterial infection evidence. Multiple indexes reflected acid-base balance were changed such as bicarbonate radical(11.8→4.8), blood pH(7.42→6.91), partial pressure of carbon dioxide(35→17), partial pressure of oxygen(83→348), although sodium bicarbonate was used.

2 Discussion

As an antineoplastic agent for treatment of various tumor types, BLM is a mixture of basic cytotoxic glycopeptide antibiotics produced by Streptomyces verticillus (BLM A_2 and BLM B_2 are the major components)[7]. Various combination chemotherapy regimens including BLM as a single dose or as a fractionated dose are used, for example, ABVD regimen for HD. Although it has the advantage of less myelotoxicity, BLM has a low therapeutic index, and prominent toxicities include

skin rashes, hypotension, pyrexia, coma and pulmonary toxicity, so the effective use of BLM is greatly limited. The primary mechanism by which BLM induces pulmonary toxicity is thought to be related to redox cycling of an iron-BLM complex that catalyzes the formation of superoxide and hydroxyl radicals and causes DNA strand scission and lipid peroxidation[8]. Pyrexia is quite common whose occurring rate is 20%−50%. The mechanism of fever production is unknown. In addition to the frequent pyretic complication, acute fulminant reactions (e.g., hypotension, mental confusion, chills, wheezing) to BLM had been described in patients with Hodgkin's or non-Hodgkin's disease[9].

Our HD patient with pulmonary tuberculosis presented a series of severe adverse reactions including hyperpyrexia, coma, vomiting, and wheezing post BLM as final administration in ABVD chemotherapy regimen. The reactions were acutely treated with epinephrine and antihistamines, but all these measures neither prevented nor substantially altered his course.

BLM-induced toxic reactions were similar to other reports from literatures, but the blood pressure was different from other reports in our case. The reduction of the blood pressure was not obvious for 15 h before shock event, and oxygen saturation and Fi O_2 concentrations undulated within the normal range that were usually considered safe. We should actively participate in rescue, but not neglect the monitoring during the illusion, especially patients >70 years of age and pulmonary complication. It is quite favorable to ascertain the type of acid base disorders on account of BLM-induced pneumonitis (BIP) during shock stage, such we can improve the success rate of rescuing by means of effective intervention measures. Metabolic acidosis with respiratory alkalosis was predominant in the present case. Finally, the patient might succumb to multiple organ failure caused by metabolic disorder under acid-base disturbance(respiratory or metabolic). Gratifying result might occur by means of timely application of sodium bicarbonate before (not after) the laboratory results.

BLM may increase sensitivity risk of anaphylactoid reactions in lymphoma patients, therefore, it is necessary to monitor patients with HD or non-Hodgkin's disease carefully and frequently during and after therapy. Dukin reported a nearly fatal reaction in a patient histiocytic lymphoma who received a test dose of 1 unit(1 mg) BLM[10]. Hyperpyrexia, shock and death following initial injection 7.5 units of BLM for a poorly differentiated metastatic carcinoma were reported[5]. It seemed likely to suggest that idiosyncratic reaction of BLM might be correlated with the individual sensitivity, not the drug doses. Therefore, it is essential to do sensitivity testing. Patients shall be administered 1 test doses (or ≤1 unit of BLM) before initiating full-dose therapy, by intravenous injection slowly over a 10 min period. Then, his/her clinician individualizes dosage carefully according to individual requirements and response, or terminate if necessary.

BLM sometimes causes fatal pulmonary toxicity, including BIP, which may further cause the risk of acute respiratory failure or lung fibrosis without timely treatment[11-12]. The development of BIP usually begins after BLM therapy, up to 6 months and even to 2 years[13]. The central event is endothelial damage of the lung vasculature due to BLM-induced cytokines and free radicals. The widely used transfer capacity of the lungs for carbon monoxide appears recently not to be specific when BLM is used in a polychemotherapeutic regimen. Up to now, there are no proven effective treatments for BIP and acute lung injury in humans, although corticosteroids are widely applied[14-15]. Dyspnea and fine rales are early manifestations, which need to be monitored carefully. Patients ought to perform chest radiographs every 1–2 weeks and sequential measurement of pulmonary diffusion capacity for carbon monoxide monthly during therapy. Significantly, timely correction of hypoxia acts as an important role in protecting the main organs by intermittent oxygen therapy.

3 Conclusion

Severe reaction to BLM may be immediated or delayed for several hours to occur with small or large doses of the drug, usually after the first or second dose. It is quite necessary to inform lymphoma patients of severe idiosyncratic reactions (hypotension, mental confusion, fever, chills, wheezing) and advise them to report any sudden onset of concomitant illnesses to clinicians. It should be recommended that the empirical 1 unit test dose is

administered after prophylactic agents. If no acute reaction occurs, recommended dosage regimen may then be administered. Treatment of anaphylactoid reactions is supportive and symptomatic and may include volume expansion, vasopressor therapy, antihistamines, and corticosteroids.

In addition, it is necessary to limit the usage of other drugs including antituberculosis drugs in the chemotherapeutic period in order to alleviate hepatorenal damage. We should never neglect the monitoring during the chemotherapy period in leukemia cases, since severe hazard event can occur in blood pressure and oxygen saturation that are usually considered safe in initial stage of administration. Blood gas analysis is useful for clinical evaluation to safety following BLM, especially for serum bicarbonate levels and arterial pH. It might be more favorable to correct acid-base balance early, for example, timely application of sodium bicarbonate. Moreover, it is very important to clean vomitus and elevate head on proper height to efficiently decrease the occurrence of aspiration, which can improve the success rate of rescuing with fewer complications.

REFERENCES

[1] DE VITA V T, LAWRENCE T S, ROSENBERG S A. Cancer: Principles and Practice of Oncology [M]. 8th Ed. Philadelphia: Lippincott William & Wilkins, 2008: 2085.

[2] BÖLL B, GÖRGEN H, FUCHS M, et al. ABVD in older patients with early-stage Hodgkin lymphoma treated within the German Hodgkin Study Group HD10 and HD11 trials [J]. J Clin Oncol, 2013, 31(12): 1522-1529.

[3] UHM J, KURUVILLA J. Treatment of newly diagnosed advanced stage Hodgkin lymphoma [J]. Blood Rev, 2012, 26(4): 167-174.

[4] EVENS A M, HONG F, GORDON L I, et al. The efficacy and tolerability of adriamycin, bleomycin, vinblastine, dacarbazine and Stanford V in older Hodgkin lymphoma patients: a comprehensive analysis from the north American intergroup trial E2496 [J]. Br J Haematol, 2013, 161(1): 76-86.

[5] LEVY R L, CHIARILLO S. Hyperpyrexia, allergic-type response and death occurring with low-dose bleomycin administration [J]. Oncology, 1980, 37(5): 316-317.

[6] SUDDEK G M, SALEM H A, BADARY O A, et al. Paracetamol supplementation does not alter the antitumor activity and lung toxicity of bleomycin [J]. J Food Pharm Sci, 2013, 2(1): 7-14.

[7] CHABNER B A, LONGO D L. Cancer Chemotherapy and Biotherapy: Principles and Practice [M]. 3th Ed. Philadelphia: Lippincott-Raven, 1996: 379-393.

[8] KAWAI K, AKAZA H. Bleomycin-induced pulmonary toxicity in chemotherapy for testicular cancer [J]. Expert Opin Drug Saf, 2003, 2(6): 587-596.

[9] BLUM R H, CARTER S K, AGRE K. A clinical review of bleomycin-a new antineoplastic agent [J]. Cancer, 1973, 31(4): 903-914.

[10] DURKIN W J. Treatment of advanced lymphomas with bleomycin(NSC-125066) [J]. Oncology, 1976, 33(3): 140-145.

[11] BERGER K, GÖPFERT A, BERKEL H. Bleomycin-induced pneumonitis [J]. Anasthesiol Intensivmed Notfallmed Schmerzther, 1996, 31(9): 577-581.

[12] VENKATESAN N, PUNITHAVATHI V, CHANDRAKASAN G. Curcumin protects bleomycin-induced lung injury in rats [J]. Life Sci, 1997, 61(6): 51-58.

[13] UZEL I, OZGUROGLU M, UZEL B, et al. Delayed onset bleomycin-induced pneumonitis [J]. Urology, 2005, 66(1): 195.

[14] SLEIJFER S. Bleomycin-induced pneumonitis [J]. Chest, 2001, 120(2): 617-624.

[15] CRAIG T R, DUFFY M J, SHYAMSUNDAR M, et al. A randomized clinical trial of hydroxymethylglutaryl–coenzyme a reductase inhibition for acute lung injury(The HARP Study) [J]. Am J Respir Crit Care Med, 2011, 183(5): 620-626.

收稿日期：2013-08-29

本刊投稿须知

本刊只接受网上投稿，步骤如下：

①登陆网址：www.chinjmap.com 点击作者在线投稿；②进行注册登陆(*为必填项)；③所投稿件如果由多位作者合写，可以点击“增加作者”，填入所有合写作者的信息(*为必填项)；④请输入对应的中英文关键词，并点击“添加”添至关键词框内，如稿件有多个关键词，请依次逐个添加；⑤您可以提供您想回避的审稿专家和建议的审稿专家，供我们参考；⑥提交成功以后，将在“待处理稿件”中显示您的稿件。若未成功则请点击“草稿箱”进行“修改并继续投稿”。⑦通过“稿件查询”可查看稿件状态，若为“审稿中”说明稿件正在外审，敬请耐心等待。