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Febrile Hypotensive Reactions Following ABVD Chemotherapy in Patients With EBV-associated Classical Hodgkin Lymphoma

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Clinical Practice Points

- ABVD (doxorubicin, bleomycin, vinblastine, and dacarbazine) is a widely used front-line regimen for the treatment of early and advanced stage classical Hodgkin lymphoma (cHL). A fulminant syndrome characterized by pyrexia and shock was observed in early trials of bleomycin, occurring more frequently in patients with lymphoma. In the past 3 decades, only 1 case of a similar fulminant reaction following ABVD had been reported, and thus there is limited literature regarding the risk factors, clinical course, and management for this life-threatening syndrome.
- We identified 3 patients experiencing febrile hypotensive reactions following ABVD chemotherapy at our institution with shared baseline clinical features, including stage IVB disease, high risk disease by International Prognostic Score, male gender, and Epstein-Barr virus-positive cHL. All 3 patients experienced fever, rigors, tachycardia, shortness of breath or hypoxia, and an elevated venous lactate with onset less than 2 hours after completing the first ABVD infusion.
- All patients received intravenous fluid resuscitations and corticosteroids, 2 patients required vasopressors owing to refractory hypotension, and 1 patient required mechanical ventilation for respiratory failure. Symptoms resolved within 24 hours in all cases.
- Two patients received bleomycin with subsequent cycles, and 1 patient was treated with AVD (doxorubicin, vinblastine, and dacarbazine); fulminant reactions were not observed with subsequent cycles.
- Clinicians should be aware that fulminant febrile hypotensive reactions can be seen following ABVD treatment for cHL. Management with intravenous corticosteroids and intensive supportive care was associated with resolution within 24 hours of onset in the present series.

Introduction

Classical Hodgkin lymphoma (cHL) comprises approximately 10% of all cases of lymphoma worldwide and is curable with multi-agent chemotherapy in the majority of cases, including in patients with advanced stage disease. The ABVD regimen (doxorubicin, bleomycin, vinblastine, and dacarbazine) is currently the most widely used front-line treatment for patients with early and advanced stage cHL, with no alternative regimen to date showing superior overall survival (OS).1,3 Patients with human immunodeficiency virus (HIV) infection have an 11-fold increased risk for cHL,4 and cHL is driven by the Epstein-Barr virus (EBV) in approximately 40% of cases, including nearly all cases associated with HIV infection.5,6 Multiple prognostic risk factors have been identified, and the International Prognostic Score (IPS) is widely used to provide risk-stratification based upon clinical risk factors in patients with advanced stage disease.7 cHL is characterized by a relatively small proportion of pathologic Reed-Sternberg (RS) cells within a reactive inflammatory milieu and is associated with a state of increased

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**Febrile Hypotensive Reactions Following ABVD**

**Table 1** Summary of Clinical Laboratory Values

| Laboratory Value (Reference Range) | Patient 1 | Patient 2 | Patient 3 |
|-----------------------------------|-----------|-----------|-----------|
| WBC (4.5-11.0 K/µL)               | 4.0       | 1.3       | 3.6       |
| ALC (1.0-4.8 K/µL)                | 0.05      | 0.2       | 0.29      |
| HGB (13.2-17.3 g/dL)              | 8.2       | 6.2       | 11.6      |
| PLT (150-400 K/µL)                | 92        | 50        | 183       |
| ESR (<15 mm/hour)                 | 24        | 43        | 68        |
| Ferritin                          | 5873      | —         | 1531      |
| Bilirubin, total (<1.5 mg/dL)     | 1.5       | 4.9       | 3.6       |
| Albumin (3.5-5.0 g/dL)            | 3.1       | 2.8       | 2.9       |
| AST (14-40 units/L)               | 247       | 20        | 33        |
| ALT (10-52 units/L)               | 122       | 34        | 48        |
| Alkaline phosphatase (units/L)    | 402       | 131       | 196       |
| Uric acid (3.5-7.0 mg/dL)         | —         | —         | —         |
| Potassium (3.5-5.0 mmol/L)        | 4.4       | 3.7       | 3.9       |
| Phosphate (2.2-4.6 mg/dL)         | 2.5       | 3.5       | 4.2       |
| CK (30-220 units/L)               | 345       | —         | —         |

Abbreviations: ABVD = Doxorubicin, bleomycin, vinblastine, and dacarbazine; ALC = absolute lymphocyte count; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatinine kinase; ESR = erythrocyte sedimentation rate; HGB = hemoglobin; PLT = platelet count; WBC = white blood cell count.

cytokine production, including increased tumor necrosis factor-α, interleukin (IL)-6, and IL-8.8,9 CD68+ macrophages are a prominent component of the tumor microenvironment. A higher proportion of CD68+ cells in the tumor microenvironment are seen in EBV-positive cHL in comparison to EBV-negative cases, and a high proportion of tumor-associated CD68+ macrophages have been associated with inferior outcomes.10,11

Bleomycin is an antibody complex derived from *Streptomyces sp.* with anti-neoplastic properties owing in part to inhibition of DNA synthesis.12 In early clinical investigation, bleomycin demonstrated single-agent activity in multiple solid organ malignancies, but the highest single-agent response rates were in Hodgkin lymphoma.13 Fever was reported in 20% to 50% of patients following single-agent bleomycin, typically occurring after the first dose, and was observed more frequently in patients with cHL compared with solid organ malignancies.14 Fever was typically self-limited, but in a review of the first 1174 patients treated with single-agent bleomycin, 4 cases of fulminant fever associated with hypotension and cardiorespiratory collapse leading to death were reported, all in patients with lymphoma. In a preclinical study, bleomycin was shown to provoke fever in a dose-dependent manner in rabbits with onset 1 to 2 hours after administration, and supernatant from cultures of human and rabbit leukocytes with bleomycin induced a febrile response with shorter latency, suggesting a cytokine-mediated effect.15 Subsequent cases of fatal or life-threatening febrile, hypotensive reactions in patients with lymphoma treated with bleomycin as part of multi-agent therapy have been reported,16-19 including a patient with a febrile, hypotensive reaction following treatment with ABVD associated with tumor lysis syndrome (TLS) and markedly elevated serum IL-6.19 Here we present 3 cases of patients with cHL experiencing fulminant febrile, hypotensive reactions shortly after their first dose of ABVD with similar baseline clinical features, including EBV-positive disease, and describe their clinical courses.

**Patients and Methods**

Cases were identified after surveying the lymphoma faculty at our institution. Institutional review board approval was obtained.

**Case Series**

**Patient 1.** Patient 1 was 51 years old at initial presentation, with progressively worsening left inguinal lymph node enlargement, fever, malaise, night sweats, and weight loss. He had no significant past medical history. Physical examination was significant for temperature of 103.4°F, palpable spleen tip 2 cm below the mid-costal margin, and a large left inguinal lymph node measuring 10 × 4 cm. Computed tomography (CT) imaging revealed splenomegaly, and enlarged periarteric, celiac, retroperitoneal, and left inguinal lymph nodes. Blood and urine cultures were collected and remained sterile; EBV polymerase chain reaction (PCR) was positive at 1,600,000 copies/mL. Other laboratory values are summarized in Table 1. Core needle biopsy of the left inguinal lymph node showed cHL, with RS cells positive for Epstein-Barr encoding region (EBER) by in situ hybridization (ISH), and CD68 staining showed a predominance of macrophages comprising over 50% of the tumor background. Bone marrow biopsy was negative for disease involvement. Positron emission tomography (PET) scan showed diffuse hypermetabolic activity in lymph nodes above and below the diaphragm as well as focal sites of increased osseous uptake, consistent with Ann Arbor stage IVB disease, with IPS risk score of 6. Intravenous ganciclovir was initiated for treatment of EBV viremia prior to starting chemotherapy.

The decision was made to begin treatment with ABVD while inpatient, with doxorubicin dose reduced by 50% (12.5 mg/m²) given bilirubin elevation (3.5 on date of treatment) and risk for reduced clearance, and vinblastine, bleomycin, and dacarbazine given at standard dosing. Vital signs at initiation of treatment were significant for temperature (T) of 97.9°F, heart rate (HR) of 87, weight 112 kg, body max index (BMI) of 33.5 kg/m², and body
gancyclovir was initiated for treatment of CMV viremia. The patient was staged as Ann Arbor stage IVB given the presence of nodes and hypermetabolic postoperative changes in the right axilla. Mildly hypermetabolic left hilar and right peri-bronchial lymph nodes were present (percentage not enumerated). PET scan showed signs prior to start of treatment were significant for T 101.9° F.

Upon outpatient evaluation, the decision was made to initiate treatment with ABVD, given at standard dosing. Vital signs prior to treatment were significant for T 99.8° F, HR 122, weight 56.0 kg, BSA 1.74, and BMI 18.2. Oral dexamethasone 12 mg was administered at 15:45, and doxorubicin, bleomycin, dacarbazine, and vinblastine were administered with bleomycin infusion completed at 17:30. At 19:00, the patient reported chest tightness, rigors, and shortness of breath; vital signs were significant for T 101.9° F, HR 155, RR of 40, and BP of 146/67. Venous lactate was elevated at 5.6; other laboratory values are summarized in Table 1. Blood cultures were collected and remained sterile, and cefepime was initiated empirically. Intravenous saline and 50 mg hydrocortisone were administered as well as hydromorphone for rigors. Symptoms rapidly improved, with normalization of lactate and resolution of fever within 6 hours. Antibiotics were discontinued after 24 hours of negative cultures. ABVD was continued with dexamethasone 20 mg premedication with subsequent infusions, and no further reactions were observed. PET scan was performed after 3 cycles to evaluate response and showed progressive disease. Platinum-based salvage therapy was initiated; the patient is currently alive receiving salvage therapy for refractory cHL.

**Patient 3.** Patient 3 was 62 years old at initial presentation, with a prior history of chronic lymphocytic leukemia (CLL) treated with 6 cycles of obinutuzumab and oltuzumab in an investigational protocol completed 3 months prior to presentation. He was diagnosed with IGVH unmutated CLL after presenting with bulky lymphadenopathy; baseline cytogenetics were positive for trisomy 12 as the sole abnormality. During treatment with obinutuzumab and oltuzumab, he experienced clinical resolution of lymphadenopathy by physical exam. At his end of therapy evaluation 3 months after his sixth cycle of treatment, he noted daily fevers as high as 103°F. Physical exam showed no evidence of lymphadenopathy. He was hospitalized for further evaluation with serum EBV PCR positive at 84,523 copies/mL; other laboratory values are summarized in Table 1. Blood and urine cultures were collected and remained sterile, and other infectious workup was negative. Bone marrow biopsy revealed a hypercellular marrow with absent CLL cells by morphology or by flow cytometry, but classical RS cells were present, positive for EBER by ISH, with increased surrounding CD68+ macrophages. PET scan showed hypermetabolic activity in cervical, mediastinal, abdominal, and pelvic lymph nodes as well as hypermetabolic liver lesions and diffuse increased uptake throughout the bone marrow. The patient was staged as Ann Arbor stage IVB Richter transformation to cHL with an IPS risk score of 5. Oral valacyclovir was initiated, and the patient was discharged from the hospital.

Upon outpatient evaluation, the decision was made to initiate treatment with ABVD, given at standard dosing. Vital signs prior to treatment were significant for T 99.5° F, HR 130, weight 92.5 kg, BSA 2.17, and BMI 26.9. At 16:20, bleomycin was administered, and dacarbazine was completed at 16:40. At 17:17, rigors were noted with temperature of 103.5° F, and inpatient admission was requested. By 18:15, confusion and lethargy were noted with T 105.5° F. Fluid resuscitation, the patient developed progressive hypotension and fluid resuscitation, the patient developed progressive hypotension; norepinephrine infusion was initiated to maintain a mean arterial BP of 65, and 20 mg intravenous dexamethasone was administered.
Hypotension quickly improved, and norepinephrine was titrated off within 12 hours of onset. Intravenous antibiotics were discontinued after blood cultures remained sterile for 48 hours, oxygen was weaned off within 24 hours, and the patient was discharged on hospital day 3. For the remaining cycles of ABVD, dexamethasone 6 mg was given for 2 days prior to treatment in addition to 12 mg on the day of treatment. The patient experienced rigors at home after cycle 1 day 15 and took 6 mg of oral dexamethasone with resolution of symptoms. No subsequent episodes were noted, and the patient completed 6 cycles of ABVD. End of therapy PET was consistent with CR, and end of therapy bone marrow biopsy was negative for cHL or CLL. Within 6 months, relapse of CLL was diagnosed by bone marrow biopsy, and the patient opted to undergo allogeneic hematopoietic cell transplant (HCT) with reduced-intensity conditioning from a haplo-identical related donor for de novo CLL because of an unidentified contaminant that is no longer present in modern bleomycin formulations with resolution of symptoms. No other clinical characteristics besides bone marrow involvement at diagnosis, HIV+ status, and history of prior CLL were noted.

### Discussion

Given the high probability of cure in cHL with front-line multi-agent chemotherapy, short-and long-term toxicities from treatment are of particular importance, and awareness of potential therapy-related toxicities and supportive management is essential. In this case series, we highlight a rare, life-threatening early complication of therapy with ABVD. All 3 cases occurred during cycle 1 day 1 of ABVD therapy, and the patients shared multiple baseline clinical characteristics including advanced stage disease, B symptoms, viremia, high risk IPS score, and EBER-positive disease (baseline characteristics summarized in Table 2). The constellation of marked pyrexia, hypoperfusion, and respiratory failure in the absence of identified bacterial infection was reported as a rare complication in early clinical trials of single-agent bleomycin, and at least 4 cases with a similar constellation of symptoms leading to fatal cardiorespiratory collapse in patients with lymphoma treated with bleomycin containing regimens were reported in the 1970s and 1980s. In a review performed in 2005 regarding the need to perform test dosing of bleomycin, the author postulated that the lack of reports of similar episodes in the 1990s or beyond may be owing to routine anti-emetic corticosteroid premedication with current bleomycin-containing regimens or that prior episodes were because of an unidentified contaminant that is no longer present in current bleomycin formulations. Since that time, there has been 1 subsequent case report of a febrile, hypotensive reaction with associated TLS within the first hour of the first ABVD infusion for cHL. This report and our series demonstrate that febrile hypotensive reactions can occur with modern bleomycin formulations and corticosteroid premedication. TLS was not evident in the 3 cases from our institution and does not appear to be prerequisite for such reactions. In our series, the time to onset was 60 to 90 minutes after completion of bleomycin infusion, which coincides with the onset of pyrexia in animal studies of single-agent bleomycin. The time course and the similarity to prior case reports following single-agent bleomycin treatment point to bleomycin as the causative agent, but it remains possible that other agents in ABVD are contributory.

Although fulminant febrile episodes were fatal in many early case reports, all 3 patients in the present series survived with resolution of symptoms within 24 hours of onset. In addition to intensive supportive care, all patients received intravenous corticosteroid treatment after onset (management summarized in Table 3). This syndrome is clinically indistinguishable from bacterial sepsis, all patients received empiric antibiotics while cultures were pending. The high fevers, cardiorespiratory collapse, and neurologic
Conclusions

Fulminant febrile, hypotensive reactions following ABVD therapy for cHL are a rare but life-threatening complication of treatment. Associated TLS is not prerequisite for such reactions. With intensive supportive care and corticosteroid treatment, all patients in the present series survived these reactions with resolution of symptoms within 24 hours of onset. Clinician awareness of this rare syndrome is essential for successful management.

Disclosure

The authors have stated that they have no conflicts of interest.

References

1. Gordon LI, Hong F, Fisher RJ, et al. Randomized phase III trial of ABVD versus Stanford V with or without radiation therapy in locally extensive and advanced-stage Hodgkin lymphoma: an intergroup study coordinated by the Eastern Cooperative Oncology Group (E2496). J Clin Oncol 2013; 31:684-91.
2. Conners JM, Jurczak W, Strauss DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin’s lymphoma. N Engl J Med 2018; 378:531-44.
3. Carde P, Karrasch M, Forpriet C, et al. Eight cycles of ABVD versus four cycles of BEACOPPescalated plus four cycles of BEACOPPBaseline in stage III to IV, International Prognostic Score >¼ 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup Trial. J Clin Oncol 2016; 34:238-36.
4. Gruel AE, van Leeuwen MT, Falster MO, Vajdic CM. Incidence of cancers in people with HIV/AIDS compared with immunosuppressed transplant recipients: a meta-analysis. Lancet 2007; 370:59-67.
5. Kuppers R. The biology of Hodgkin’s lymphoma. Nat Rev Cancer 2009; 9:15-27.
6. Carbogn A, Ciglietto A, Caruso A, De Paoli P, Dolcetti R. The impact of EBV and HIV infection on the microenvironmental niche underlying Hodgkin lymphoma pathogenesis. Int J Cancer 2017; 140:1233-45.
7. Hasenclever D, Diehl V. A prognostic score for advanced Hodgkin’s disease. International Prognostic Factors Project on Advanced Hodgkin’s Disease. N Engl J Med 1998; 339:1506-14.
8. Jucker M, Abts H, Li W, et al. Expression of interleukin-6 and interleukin-6 receptor in Hodgkin’s disease. Blood 1991; 77:2413-8.
9. Klein S, Jucker M, Diehl V, Tesch H. Production of multiple cytokines by Hodgkin’s disease derived cell lines. Hematol Oncol 1992; 10:319-29.
10. Steidl C, Lee T, Shah SP, et al. Tumor-associated macrophages and survival in classic Hodgkin’s lymphoma. N Engl J Med 2010; 362:873-85.
11. Tan KL, Scott DW, Hong F, et al. Tumor-associated macrophages predict inferior outcomes in classic Hodgkin lymphoma: a correlative study from the E2496 Intergroup trial. Blood 2012; 120:5280-7.
12. Umezawa H, Iizuka M, Maeda K, Takeuchi T. Studies on bleomycin. Cancer 1967; 20:893-5.
13. Yagoda A, Mukherji B, Young C, et al. Bleomycin, an antitumor antibiotic. Clinical experience in 274 patients. Ann Intern Med 1972; 77:861-70.
14. Blum RH, Carter SK, Agre K. A clinical review of bleomycin—an new antineoplastic agent. Cancer 1973; 31:901-14.
15. Dinarello CA, Ward SB, Wolf M. Myeloperoxidase of bleomycin (NSC-125066). Cancer Chemother Rep 1973; 57:393-8.
16. Rosenfeld F, Palmer J, Weinstein I, et al. Bleomycin, an antitumor antibiotic. An analysis of new antineoplastic agents. Cancer 1973; 31:901-14.
17. Suzuki T, Takeuchi M, Saeki H, et al. Super-acute onset of tumor lysis syndrome following bleomycin treatment is clinically similar to the tachyphylactic syndrome following bleomycin treatment. Int J Cancer 1982; 29:529-31.
18. Jagoda A, Mukherji B, Young C, et al. Bleomycin, an antitumor antibiotic. Clinical experience in 274 patients. Ann Intern Med 1972; 77:861-70.
19. Blum RH, Carter SK, Agre K. A clinical review of bleomycin—an new antineoplastic agent. Cancer 1973; 31:901-14.
26. Behringer K, Goergen H, Hitz F, et al. Omission of dacarbazine or bleomycin, or both, from the ABVD regimen in treatment of early-stage favourable Hodgkin’s lymphoma (GHSG HD13): an open-label, randomised, non-inferiority trial. *Lancet* 2015; 385:1418-27.

27. Johnson P, Federico M, Kirkwood A, et al. Adapted treatment guided by interim PET-CT scan in advanced Hodgkin’s lymphoma. *N Engl J Med* 2016; 374:2419-29.

28. Weiss LM, Movahed LA, Warnke RA, Sklar J. Detection of Epstein-Barr viral genomes in Reed-Sternberg cells of Hodgkin’s disease. *N Engl J Med* 1989; 320:502-6.

29. Chetaille B, Bertucci F, Finetti P, et al. Molecular profiling of classical Hodgkin lymphoma tissues uncovers variations in the tumor microenvironment and correlations with EBV infection and outcome. *Blood* 2009; 113:2765-77.

30. Teichmann M, Meyer B, Beck A, Niedobitek G. Expression of the interferon-inducible chemokine IP-10 (CXCL10), a chemokine with proposed anti-neoplastic functions, in Hodgkin lymphoma and nasopharyngeal carcinoma. *J Pathol* 2005; 206:68-75.

31. Baumforth KR, Birgersdotter A, Reynolds GM, et al. Expression of the Epstein-Barr virus-encoded Epstein-Barr virus nuclear antigen 1 in Hodgkin’s lymphoma cells mediates up-regulation of CCL20 and the migration of regulatory T cells. *Am J Pathol* 2008; 173:195-204.

32. Morales O, Mitzak D, Francois V, et al. Epstein-Barr virus infection induces an increase of T regulatory type 1 cells in Hodgkin lymphoma patients. *Br J Haematol* 2014; 166:875-90.

33. Maude SL, Barrett D, Teachey DT, Grupp SA. Managing cytokine release syndrome associated with novel T cell-engaging therapies. *Cancer J* 2014; 20:119-22.