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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.

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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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Table 1 Summary of Clinical Laboratory Values

Laboratory Value (Reference Range)	Patient 1		Patient 2		Patient 3	
	Baseline	Post ABVD	Baseline	Post ABVD	Baseline	Post ABVD
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	1.1	3.6	0.7	–
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)		5.9		–		–
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 periaortic, 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/m^2) 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/m^2, and body

surface area (BSA) of 2.33. Twelve mg oral dexamethasone was given at 15:10, and the bleomycin infusion was completed at 16:10. At 17:30, rigors were noted with temperature of 102.1°F. Hydrocortisone 50 mg and 1 L of normal saline were administered, but ongoing rigors and hyperthermia were noted with T 105.5°F, HR 160, respiratory rate (RR) 44, and blood pressure (BP) 133/77. Venous blood lactate was elevated at 4.4, and the patient was intubated emergently for worsening encephalopathy. Shortly after intubation, the patient became hypotensive, and intravenous norepinephrine via continuous infusion was initiated along with further intravenous hydration. Blood cultures were drawn and empiric broad-spectrum antibiotics initiated. Chest radiograph was negative for consolidation or infiltrate. Other laboratory values are summarized in Table 1. Vasopressors were weaned off within 12 hours, and the patient was extubated within 24 hours. Bleomycin was omitted from further cycles without subsequent complications. After 6 cycles of treatment, PET imaging was consistent with complete response (CR). The patient remains in follow-up with no evidence of relapse over 3 years after completion of therapy.

Patient 2. Patient 2 was 28 years old at diagnosis with a history of HIV infection treated with anti-retroviral therapy; baseline CD4 count was 287 cells/mm^3 with an undetectable HIV viral load. He presented with fever, shortness of breath, and a dry cough. Physical examination was significant for dry mucous membranes, diminished breath sounds bilaterally, and an enlarged right axillary lymph node. Baseline laboratory values are summarized in Table 1. CT scan of the chest revealed bilateral airspace consolidation and an enlarged right axillary lymph node. Bone marrow biopsy was performed and was interpreted as nondiagnostic with necrotizing granulomas noted. The patient was intubated on hospital day 3 for worsening respiratory status and diagnosed with acute respiratory distress syndrome. Bronchiolar lavage was consistent with pneumocystis pneumonia, and treatment with methylprednisolone and trimethoprim/sulfamethoxazole was initiated. On hospital day 14, the patient was extubated, and the following day, an excisional right axillary lymph node biopsy was performed that was consistent with cHL, and the patient was transferred to our hospital for further care. The prior bone marrow biopsy was reviewed by hematopathology at our institution and read as consistent with cHL with extensive necrosis with scattered fibro-histiocytic infiltrates containing typical RS cells, positive for EBER by ISH, and numerous CD68+ macrophages present (percentage not enumerated). PET scan showed mildly hypermetabolic left hilar and right peri-bronchial lymph nodes and hypermetabolic postoperative changes in the right axilla. The patient was staged as Ann Arbor stage IVB given the presence of bone marrow involvement, with IPS risk score of 5. Oral valgancyclovir was initiated for treatment of CMV viremia.

Therapy was initiated with ABVD given at standard dosing. Vital signs prior to start of 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 otlertuzumab 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 otlertuzumab, 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 106°F, HR 144, BP 92/53, and RR 27. Hydrocortisone was administered intravenously (50 mg) as well as oral acetaminophen and normal saline hydration. The patient developed progressive hypoxia with requirement of 13L oxygen by high-flow nasal canula; chest radiograph demonstrated a pulmonary edema pattern bilaterally. Blood and urine cultures were collected and remained sterile, and an extended respiratory viral panel returned positive for coronavirus. Other laboratory values are summarized in Table 1. Despite 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.

Table 2 Summary of Baseline Patient Characteristics

	Patient 1	Patient 2	Patient 3
Age at diagnosis, y	51	28	62
Gender	M	M	M
Stage at diagnosis	IVB	IVB	IVB
Viremia detected at diagnosis	Yes, EBV	Yes, CMV	Yes, EBV
EBER ISH status	Positive	Positive	Positive
EBV viral load PCR, copies/mL	1,632,495	< 2000	84,523
Description of CD68+ macrophage staining on diagnostic biopsy	> 50%	"Numerous"	"Increased"
Other clinical characteristics	Bony involvement at diagnosis	HIV+	History of prior CLL
Marrow involvement on BMBX	No	Yes	Yes
IPS risk score	6	5	5

Abbreviations: BMBX = Bone marrow biopsy; CLL = chronic lymphocytic leukemia; CMV = cytomegalovirus; EBER ISH = EBV encoding RNA in situ hybridization; EBV = Epstein Barr virus; HIV = human immunodeficiency virus; IPS = International Prognostic Factors Project Score; PCR = polymerase chain reaction.

Table 3 Summary of Clinical Course and Treatment

	Patient 1	Patient 2	Patient 3
Premedication	Dexamethasone 12 mg	Dexamethasone 12 mg	Dexamethasone 12 mg
Time from completion of bleomycin to onset of symptoms, min	90	80	60
Symptoms at onset	Rigors, fever	Rigors, chest tightness, shortness of breath	Rigors, confusion, lethargy
Tmax (°F)	105.5	101.9	103.5
Peak lactate, mmol/L	4.4	5.6	1.6
Hemodynamic supportive care	IV fluids, norepinephrine infusion	IV fluids	IV fluids, norepinephrine infusion
Corticosteroid treatment	Hydrocortisone 50 mg	Hydrocortisone 50 mg	Hydrocortisone 100 mg and dexamethasone 20 mg
Respiratory support	Mechanical ventilation	None	High-flow oxygen by nasal canula
Time to resolution of symptoms, h	12	6	24
Bleomycin given with subsequent cycles	No	Yes	Yes
Response to treatment	CR	PD	CR

Abbreviations: CR = Complete response; F = Fahrenheit; IV = intravenous; PD = progressive disease; Tmax = maximum temperature.

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 definitive treatment of CLL and to mitigate the risk of relapse of Richter transformation to cHL. He remains alive in active follow-up with no evidence of relapse of CLL or cHL over 12 months after HCT.

Discussion

Given the high probability of cure in cHL with front-line multiagent 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,[14] 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.[16-18,20] 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.[21] 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.[19] 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.[15] 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,[16-18,20] 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). As this syndrome is clinically indistinguishable from bacterial sepsis, all patients received empiric antibiotics while cultures were pending. The high fevers, cardiorespiratory collapse, and neurologic

symptoms seen in this series and prior reports are similar to the cytokine release syndrome (CRS) seen following bispecific antibody and chimeric antigen receptor T cell therapy.[22-24] Multiple cytokines have been implicated in CRS, including interferon-γ, IL-10, and IL-6, and monoclonal antibodies targeting the IL-6/IL-6 receptor axis such as tocilizumab are used for CRS treatment,[24,25] Marked elevation of serum IL-6 was noted in the case report by Suzuki et al,[19] but to our knowledge, tocilizumab has not been used in the context of bleomycin-associated febrile, hypotensive reactions, and in all cases in the present series, symptoms resolved rapidly following corticosteroid treatment.

Given the rarity of this syndrome, the safety of bleomycin rechallenge is not well-defined. Bleomycin was omitted from subsequent cycles for Patient 1, but Patient 2 and 3 tolerated bleomycin in subsequent cycles with increased steroid premedication. Although bleomycin does contribute to the activity of ABVD, it is the least active agent in the combination regimen[26] and can be safely omitted from cycles 3 to 6 of therapy for patients with advanced stage disease with negative interim PET imaging.[27] The substitution of brentuximab vedotin for bleomycin (A-AVD) was compared with ABVD in patients with stage III/IV cHL in the phase III ECHELON-1 study, and resulted in a statistically significant improvement in the primary endpoint of modified progression-free survival at 2 years with no difference in OS at the time of analysis.[2] A-AVD is approved by the United States Food and Drug Administration for front-line treatment of advanced stage cHL and would be an alternative consideration to bleomycin rechallenge or AVD therapy for advanced stage patients experiencing fulminant hyperpyrexia during cycle 1 of ABVD.

The shared clinical characteristics of the patients in our series may shed light on the pathophysiology of this rare syndrome. As in prior reports, all patients in the present series were febrile prior to the start of therapy and presented with advanced stage disease. As bleomycin can induce fever presumably through cytokine-mediated stimulation,[15] one possible explanation is that febrile patients have increased baseline levels of key cytokines, and the additive effect of cytokine stimulation by bleomycin crosses a threshold, triggering a fulminant reaction.[17] Other common features of all 3 patients in this series include EBV+ disease and increased CD68+ tumor associated macrophages, and to our knowledge, this represents a novel observation not noted in prior case reports. The majority of prior reports occurred before the development of standard of care ISH testing for EBER[28] or routine CD68 staining, and thus it is unknown whether prior cases shared these common features. In comparison to EBV-negative cHL, EBV-positive disease has been associated with a gene expression signature of macrophage response including upregulation of *CXCL10*, *CCL5*, *CD14*, *CD68*,[29,30] regulatory T cell type 1 recruitment including upregulation of *CCL20*[31] and *LAG3*,[32] and altered cytokine signaling with upregulation of *IL10*, *TGFB-1*, *IFNG*, and *TNF*.[32] The febrile, hypotensive syndrome following bleomycin treatment is clinically similar to CRS, a syndrome in which macrophage activating cytokines IL-10 and IL-6 are elevated, and macrophage activation appears to be central to pathogenesis.[33] The mechanism of fulminant febrile hypotensive reactions following bleomycin requires further elucidation, including determining the role of macrophage activation.

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 RI, 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. Connors JM, Jurczak W, Straus DJ, et al. Brentuximab vedotin with chemotherapy for stage III or IV Hodgkin's lymphoma. *N Engl J Med* 2018; 378:331-44.
3. Carde P, Karrasch M, Fortpied 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 >/= 3, high-risk Hodgkin lymphoma: first results of the phase III EORTC 20012 Intergroup Trial. *J Clin Oncol* 2016; 34:2028-36.
4. Grulich 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. Carbone A, Gloghini 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; 362:875-85.
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; 120:3280-7.
12. Umezawa H, Ishizuka M, Maeda K, Takeuchi T. Studies on bleomycin. *Cancer* 1967; 20:891-5.
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–a new antineoplastic agent. *Cancer* 1973; 31:903-14.
15. Dinarello CA, Ward SB, Wolff SM. Pyrogenic properties of bleomycin (NSC-125066). *Cancer Chemother Rep* 1973; 57:393-8.
16. 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; 55:529-31.
17. Carter JJ, McLaughlin ML, Bern MM. Bleomycin-induced fatal hyperpyrexia. *Am J Med* 1983; 74:523-5.
18. Leung WH, Lau JY, Chan TK, Kumana CR. Fulminant hyperpyrexia induced by bleomycin. *Postgrad Med J* 1989; 65:417-9.
19. Suzuki T, Takeuchi M, Saeki H, et al. Super-acute onset of tumor lysis syndrome accompanied by hypercytokinemia during treatment of Hodgkin's lymphoma with ABVD chemotherapy. *Clin Ther* 2010; 32:527-31.
20. Ma DD, Isbister JP. Cytotoxic-induced fulminant hyperpyrexia. *Cancer* 1980; 45: 2249-51.
21. Lam MS. The need for routine bleomycin test dosing in the 21st century. *Ann Pharmacother* 2005; 39:1897-902.
22. Topp MS, Gokbuget N, Stein AS, et al. Safety and activity of blinatumomab for adult patients with relapsed or refractory B-precursor acute lymphoblastic leukaemia: a multicentre, single-arm, phase 2 study. *Lancet Oncol* 2015; 16: 57-66.
23. Porter DL, Levine BL, Kalos M, Bagg A, June CH. Chimeric antigen receptor-modified T cells in chronic lymphoid leukemia. *N Engl J Med* 2011; 365:725-33.
24. Klinger M, Brandl C, Zugmaier G, et al. Immunopharmacologic response of patients with B-lineage acute lymphoblastic leukemia to continuous infusion of T cell-engaging CD19/CD3-bispecific BiTE antibody blinatumomab. *Blood* 2012; 119:6226-33.
25. Grupp SA, Kalos M, Barrett D, et al. Chimeric antigen receptor-modified T cells for acute lymphoid leukemia. *N Engl J Med* 2013; 368:1509-18.

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; 113:2765-3775.
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, Mrizak 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.