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Incidence and Predictors of Pulmonary Events among Patients with Hodgkin Lymphoma Treated with Bleomycin in the US Department of Defense Healthcare System

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Abstract

Objectives: Multi-agent chemotherapy including bleomycin, doxorubicin, dacarbazine, and vinblastine has been the standard of care for initial treatment of Hodgkin Lymphoma (HL) for over 40 y. The study objective was to estimate the rate of new pulmonary events in HL patients exposed to bleomycin.

Methods: A retrospective cohort study supplemented by chart abstraction included newly diagnosed adult HL patients from the US DOD military healthcare system between 1/1/2005 and 12/31/2013 and followed until death, disenrollment on 6/30/2016. Patients with concurrent primary malignancies and those receiving <2 chemotherapy agents as first-line treatment were excluded. Pulmonary events (pulmonary fibrosis, pneumonitis, interstitial lung disease, pneumonia, bronchiolitis obliterans, acute respiratory distress syndrome) after exposure to bleomycin ± RT were identified through ICD-9/10 codes from the electronic medical records. Logistic regression and Cox proportional hazards models were developed to identify predictors of the first new pulmonary event and time to a new event.

Results: A total of 642 HL patients were identified, mean age (SD) of 32 y (13.0), 67% male, 35% stage 3/4 at diagnosis. Bleomycin was administered to 85.8% of patients, and 30% of these experienced new pulmonary events. For those treated with bleomycin, 9.4% experienced new pulmonary events up to 6 months after exposure and an additional 13.8% between 7-24 months and 5.1% between 24-48 months after bleomycin exposure. Logistic regression and Cox proportional hazards model fit results were modest. Significant predictors were age and number of doses of bleomycin; however, pulmonary events could not be predicted by the number of bleomycin doses received since the probability peaked after 4 doses.

Conclusions: This analysis demonstrates that HL patients may experience a new pulmonary event up to 2 y after receiving initial treatment containing bleomycin. The incidence of pulmonary events associated with bleomycin was difficult to predict in this patient population.

Keywords: Bleomycin; Department of defense; Hodgkin lymphoma; Pulmonary events; Radiation therapy; United States

Introduction

Multi-agent chemotherapy including doxorubicin, bleomycin, vinblastine, and dacarbazine (ABVD) in the United States, with or without radiation therapy has been the standard of care for initial treatment of HL for over 40 y [1,2]. There were approximately 8,260 new cases of HL and about 1,070 deaths due to HL estimated in 2017 [3]. Recent advancements in initial treatment strategies have focused on the minimization of toxicity through chemotherapy de-escalation [4,5] but have failed to show non-inferiority [4,6]. Data on cancer survivors have revealed acute and delayed modality-specific toxicities and susceptibility to long-term adverse effects from chemotherapeutic agents [7,8]. A key issue for HL survivors is latent toxicity, which includes secondary malignancies [9-11] and cardiovascular complications [12-14], while pulmonary effects can be both acute and/or long-term [15-17].

Bleomycin Pulmonary Toxicity (BPT) has been well described in HL patients treated with bleomycin-containing regimens [18]. Bleomycin can induce interstitial pneumonitis that may progress to severe fibrosis, which may result in premature death for some patients [19,20]. Radiation therapy and Granulocyte Colony-Stimulating Factor (G-CSF) may potentiate or increase the risk of toxicity after concurrent exposure to bleomycin [17,21,22] although this has not been confirmed. The reported rate of toxicity after bleomycin exposure ranges from 1% to 46% among HL patients, depending on toxicity definition and population studied [20-23], with mortality as high as 27% [24-26]. Acute pulmonary events include shortness of breath, interstitial infiltrates and inflammation, pneumonitis, and acute pneumonia while long-term effects include pulmonary fibrosis [16]. BPT may result in long-term morbidity for patients who were otherwise cured of HL. Therefore, it is important to understand the current rate of BPT among HL patients to understand the full incidence of short-term pulmonary events and long-term events associated with prior bleomycin exposure. The objectives of this analysis were to describe the burden of bleomycin exposure among newly diagnosed HL patients who were treated in the US Department of Defense (DOD) healthcare system, estimate the incidence of pulmonary events and evaluate predictors of an association between bleomycin exposure and new pulmonary events.

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Methods

This retrospective cohort study utilized Electronic Medical Records (EMR) supplemented with chart review to evaluate the association of bleomycin-containing therapy with the occurrence of new pulmonary events among HL patients treated in the US DOD healthcare system. The DOD healthcare system is a large, single-payer integrated delivery network that has 10 million active beneficiaries, over 65 hospitals, 500 military clinics, and civilian hospitals and clinics throughout the US *via* the TRICARE network. The study used data from the Military healthcare system data repository electronic medical records, the automated central tumor registry, and the pharmacy data transaction system database which included prescribing data for both direct military care and purchased care (outpatient, inpatient, and mail order). The DOD healthcare databases included active duty military, retirees, their dependents and are considered to be representative of the general US population for age and race [27]. This research was approved by the Naval Medical Center Portsmouth, VA Institutional Review Board with an exemption for patient consent.

Newly diagnosed adult (≥ 18 years of age) HL patients, stages 1-4, between January 1, 2005 and December 31, 2013 were included in the study if they had no other primary malignancy except for basal cell skin cancer and their frontline chemotherapy included more than 1 agent. Index date was date of diagnosis of HL, and patients were followed from date of diagnosis until death, disenrollment, or end of study (June 30, 2016), whichever occurred first.

Exposure was defined as treatment with bleomycin as part of the initial treatment regimen. The number of doses of bleomycin administered during frontline and subsequent lines of therapy was calculated from the pharmacy data based on dates of administration and regimen type. A new line of therapy was defined as the start of a new chemotherapy agent or occurrence of stem cell transplant. Chemotherapy regimens were classified based upon the most common individual agents administered and a list of the ABVD/ABVD variant regimens is found in Appendix A. A pulmonary event was defined as a new event after the first dose of bleomycin was administered. Pulmonary events occurring between diagnosis date and first bleomycin dose were not counted. Pulmonary events were identified through ICD 9/10 codes in the EMR, based on a literature search and expert clinical experience from a hematologist/oncologist, and listed in Appendix B. Incidence of a new pulmonary event was calculated as the total number of new cases divided by the number of patients in the specified time period (e.g. 0-12 months). Multivariable logistic regression was used to identify predictors for the occurrence of a new pulmonary event, and Cox proportional hazards model evaluated predictors for the time to the first pulmonary event. Independent variables in the models included number of bleomycin doses, HL stage, presence of B symptoms, age, sex, race, concurrent radiation therapy, year of diagnosis, use of G-CSF, number of comorbid conditions, patient history of cancer, family history of cancer, and prior history of pulmonary disease. Subgroup analysis was conducted among patients with HL stage 3 or 4 to understand whether the association between bleomycin and pulmonary events differed for advanced stage patients, and among patients with and without concomitant radiation therapy.

Results

Of the 767 HL patients identified in the DOD tumor registry system between 1/1/2005 and 12/31/2013, 701 were newly diagnosed during this time period and 642 were eligible and included in the study (Figure 1). HL stage 3-4 patients comprised 35% of the eligible patients. The study population was young (mean age of 32 y), 67% male, and 73% white (Table 1). Patients with HL stages 3-4 had similar demographic and clinical characteristics, except for the presence of B symptoms (56% of HL stages 3-4 *vs.* 39% of all stages). Median follow-

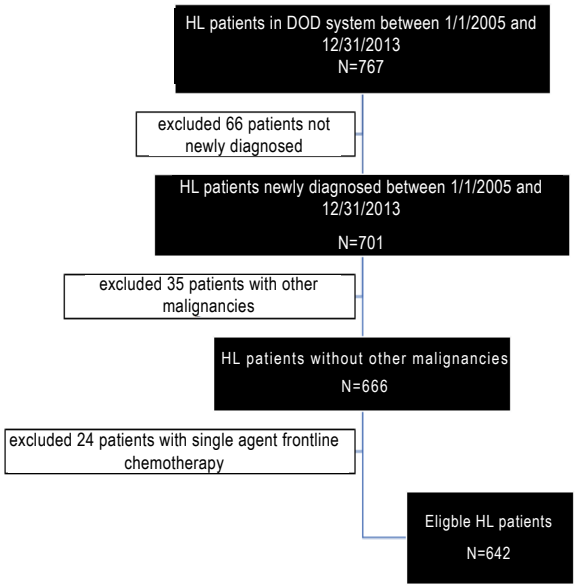

Figure 1: Hodgkin lymphoma patient eligibility criteria.

Characteristics	All HL stages n=642	HL Stage 3-4 n=224
Age, y, mean (SD), [median]	31.6 (12.97) (27.0)	33.8 (15.12) (28.0)
Male, n (%)	429 (66.8)	161 (71.9)
Race, n (%)		
White	470 (73.2)	158 (70.5)
Black	102 (15.9)	45 (20.1)
Other/unknown	70 (10.9)	21 (9.4)
Hispanic, n (%)	50 (7.8)	18 (8.0)
Beneficiary category, n (%)		
Active duty	18.8	16.1
Dependents of active duty	11.2	9.4
Retirees	27.9	29.9
Dependents of retiree	15	13.8
Other categories	27	30.8
HL Stage 1-2, n (%)	383 (59.6)	0
HL Stage 3-4, n (%)	224 (34.9)	224 (100.0)
HL stage unknown, n (%)	35 (5.5)	0
B symptoms, n (%)	248 (38.6)	125 (55.8)
History of cancer, %	2.6	4.5
Comorbidity, %		
History of pulmonary disease	4.7	4.9
Asthma	7.8	7.1
Mixed connective tissue disorder	0.9	1.3
Essential thrombocythemia	0.8	1.3
Polycythemia vera	0.5	0.4
Myeloproliferative neoplasm	0.3	0.9
Systemic lupus erythematosus	0.3	0
Aplastic anemia	0.2	0.4

Table 1: Demographic and clinical characteristics of newly diagnosed Hodgkin lymphoma patients.

up time was 4.7 y (minimum=0.06, maximum=11.96) for all HL stages and 4.4 y (minimum=0.19, maximum=11.77) for HL stages 3-4.

There were 64 patients who did not receive chemotherapy within the DOD healthcare system and were not included in subsequent analyses. Of the 578 patients who received frontline chemotherapy, 91.0% received ABVD/ABVD variant therapy.

A total of 92 patients (15.9% of those in frontline) had a second line of chemotherapy, with 29 patients (31.5%) receiving ABVD/ABVD variant regimen. Third line or subsequent chemotherapy was received by 33 patients (35.9% of those in second line). A total of 90 patients (14%) had a stem cell transplant during their treatment. Bleomycin was administered to 95% of patients in frontline therapy (median doses=8) and 33% of patients in second line (median doses=4.5) (Table 2). For patients with HL stages 3-4, 96% received bleomycin in frontline (median doses=10) and 19% in second line (median doses=8).

Incidence of pulmonary event

Cumulatively over the total follow-up period, 30% of patients treated with bleomycin had a new pulmonary event among all stages and for stages 3-4 (Figure 2). Most patients (25% among all stages and 24% of stages 3-4) experienced the pulmonary event during the first 24 months after the first bleomycin dose.

Based on non-mutually exclusive categories (patients could have more than one event), the most frequent type of pulmonary event was acute respiratory distress syndrome/pulmonary edema (n=155, 95% of patients with a pulmonary event). Post-inflammatory pulmonary fibrosis occurred in 16 (9.8%) patients while bronchopneumonia and idiopathic fibrosing alveolitis occurred in 8 (4.9%) and 5 (3.1%) patients, respectively.

Predictors of bleomycin-associated pulmonary events

A series of logistic regression models were developed to identify predictors of bleomycin-associated pulmonary events, using demographic and clinical characteristics of the HL patients. Bivariate analyses of occurrence of a new pulmonary event and each characteristic were used to identify potential predictors for inclusion in the multivariable models. Candidate predictors included number of bleomycin doses, age at diagnosis, sex, race, patient and family history of cancer, radiation treatment, number of comorbidities, use of GCSF, history of pulmonary toxicities and presence of B-symptoms. Of these, only age at diagnosis and number of bleomycin doses received (non-linear) were significant predictors of a new pulmonary event using a traditional significance level of $p<0.05$.

The best fitting model (Table 3) had a modest area under the ROC curve of 0.65. The association between occurrence of pulmonary event and number of bleomycin doses was non-linear. The probability of a pulmonary event peaked at 4 bleomycin doses then declined until 10 doses and increased with doses greater than 10 (Figure 3).

The Cox proportional hazards model also indicated that total number of bleomycin doses received, and age were significant predictors of the time to a new pulmonary event (Table 4). The model fit was modest with the model explaining only 12% of the variation. The same non-linear association with total number of bleomycin doses was observed in the Cox model.

The regression models for HL stages 3-4 excluded race, sex and patients' history of cancer due to the reduced sample size. Again, only age and number of bleomycin doses were found to be significant predictors for HL stages 3-4 patients, with the same nonlinear pattern for bleomycin doses (data not shown).

	All HL stages			HL Stages 3-4		
Line of therapy	Number of patients	Median bleomycin dose	IQR	Number of patients	Median bleomycin dose	IQR
1L	547	8	43440	197	10	43441
2L	30	4.5	43313	7	8	43405
3L	3	1	43252	1	1	1

Table 2: Bleomycin exposure.

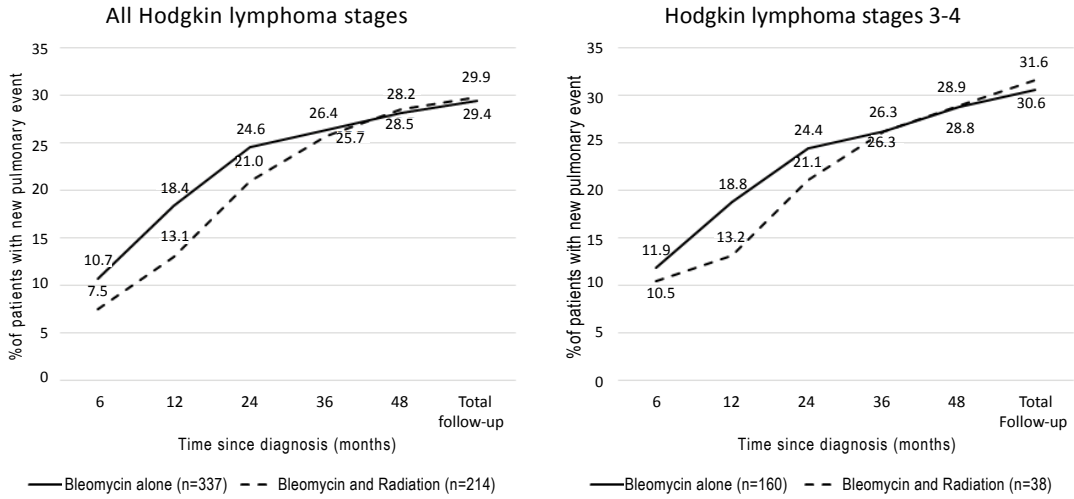

Figure 2: Cumulative incidence rate of pulmonary events after bleomycin exposure.

Predictors	Coefficient	SE	Chi-square	P value
Doses of bleomycin			28.89	<0.0001
0-4 (reference category)				
5-8 doses	0.6029	0.2692		
9-11 doses	0.1471	0.3234		
12-16 doses	0.1172	0.3029		
Age at diagnosis	0.0378	0.0087	19.01	<0.0001
Gender: female	0.1742	0.2209	0.62	0.4303
Race (White is reference category)			2.2	0.3331
Black	0.3738	0.2787		
Other	-0.1306	0.3385		
Family history of cancer	0.3065	0.2095	2.14	0.1435
Concurrent radiation therapy	-0.2251	0.2219	1.03	0.3105
Number of comorbid conditions	0.2648	0.2666	0.99	0.3205
Use of GCSF	0.1842	0.2997	0.38	0.5387
History of pulmonary disease	-0.7344	0.551	1.78	0.1826
B symptoms	0.4212	0.2137	3.89	0.0487

Table 3: Logistic regression of pulmonary events after exposure to bleomycin.

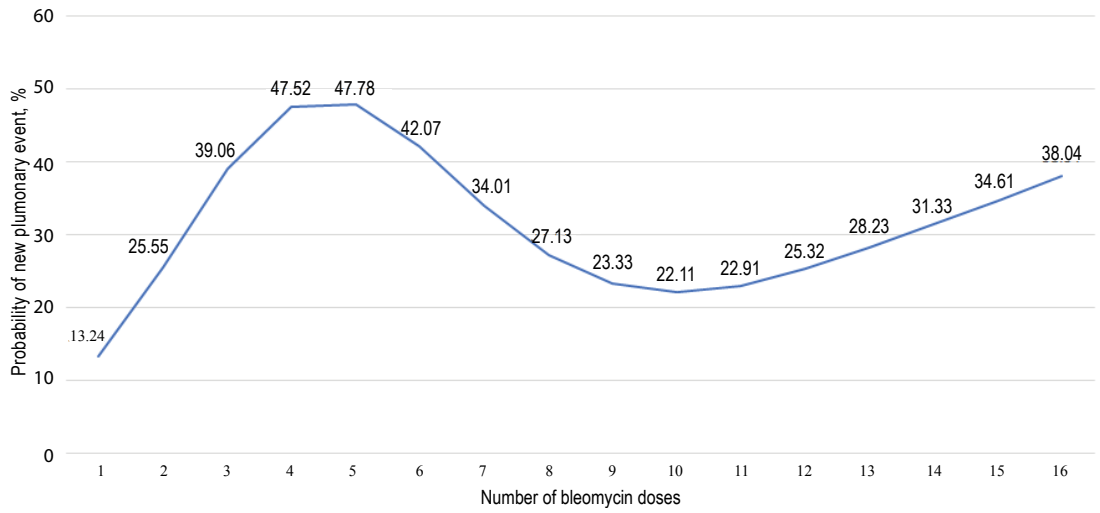

Figure 3: Probability of new pulmonary event after bleomycin exposure, by bleomycin dose after adjustment for covariates.

Predictors	Coefficient	SE	Chi-square	P value
Doses of bleomycin			29.62	<0.0001
0-4 (reference category)				
5-8 doses	0.3786	0.2234		
9-11 doses	-0.0921	0.2737		
12-16 doses	-0.1504	0.2572		
Age at diagnosis	0.0291	0.0066	19.19	<0.0001
Gender: Female	0.0688	0.189	0.13	0.7158
Race (White is reference category)			2.13	0.3454
Black	0.2879	0.2287		
Other	0.2748	0.2917		
Family history of cancer	0.2736	0.1754	2.43	0.1188
Concurrent radiation therapy	-0.3745	0.1938	3.74	0.0533
Number of comorbid conditions	0.2581	0.2039	1.6	0.2055
Use of GCSF	0.1851	0.2384	0.6	0.4375
HL stage 3-4	0.175	0.1898	0.85	0.3564
History of pulmonary disease	-0.5329	0.4703	1.28	0.2572
B symptoms	0.2641	0.1786	2.19	0.1393

Table 4: Cox proportional hazards model for time from bleomycin exposure to first pulmonary event.

Discussion

In this DOD population of HL patients, a high proportion (30%) experienced a new pulmonary event after receiving bleomycin, most often within the 24 months after the first dose of bleomycin. However, very few characteristics were associated with the occurrence or timing of the pulmonary event. Older age was a significant predictor of increased risk of a pulmonary event while the total number of bleomycin doses received showed a complex relationship with this outcome. Yet, the model fit was modest for both the logistic regression and Cox proportional hazards models, indicating that the covariates (up to 11) did not explain the occurrence or time of a pulmonary event.

The non-linear association between pulmonary events and bleomycin dose may reflect clinical practice where patients who are predisposed to pulmonary complications will experience a pulmonary event after fewer bleomycin doses (4-5 doses) compared with patients without a predisposition. Thus, this non-linear association may be real. Other explanations for the pattern may include unmeasured confounding from other characteristics that were not available in the EMR such as smoking status, performance status or immunogenicity at diagnosis. It is important to note that the association with pulmonary events increased with 1-4 doses of bleomycin which is lower exposure than the strategies employed in recent clinical trials. The RATHL study employed PET-CT scanning after 2 cycles of ABVD chemotherapy with de-escalation of treatment to AVD or continued 4 cycles of ABVD for patients with a negative PET scan [4,28]. The omission of bleomycin in the RATHL study following a negative interim PET reduced acute pulmonary toxicity [4] but the present study indicates that pulmonary events may occur even before the end of cycle 2 (4^{th} dose). This is important since pulmonary events impact subsequent health outcomes and are associated with mortality [24,25,29]. The recent ECHELON-1 trial [26] found that 11 of the 13 deaths occurring during ABVD treatment were associated with pulmonary-related toxicity.

The study findings are similar to previous investigations of bleomycin-associated pulmonary events. Several studies reported the incidence of pulmonary events in 18% to 31% of HL patients who received bleomycin-containing chemotherapy [17,18,24,25,30]. In a post hoc analysis of a randomized clinical trial, Haverkamp et al. [30] reported that 24.8% of newly diagnosed advanced HL patients experienced a pulmonary event. In a retrospective chart review, Stamatoullas et al. [25] reported that 21% of HL patients treated with ABVD had a pulmonary event, with 4.8% being fatal. Other studies have reported lower incidence rates of pulmonary events (5%-12%) among HL patients treated with ABVD but these studies used different methods to define pulmonary events [1,21]. In the ECHELON-1 trial, pulmonary toxicity of grade 3 or higher was reported in 3% of patients receiving ABVD [26]. The majority of these studies focused on acute adverse pulmonary effects of bleomycin during a short time period (mostly while on treatment during the clinical trial); however, it is important to note that pulmonary events may occurs year after treatment with bleomycin and may not be currently followed by the physician who administered the therapy. In the present study, patients exposed to bleomycin were followed for new pulmonary events for up to 4 y *via* their EMR and even though the majority of events occurred in the first 24 months, HL patients did experience a new pulmonary event through 48 months.

Few studies have investigated risk factors for bleomycin-associated pulmonary toxicity, and similar to this study, they did not find any factors explaining the risk of pulmonary events. Evens et al. [24] evaluated demographics, ejection fraction, and lung function variables and found no factors predicting BPT. Likewise, Stamatoullas et al. [25] investigated age, renal status, prior lung disease, tobacco history, G-CSF use, and radiotherapy as potential predictors for pulmonary toxicity among patients who received bleomycin and found no significant impact from any risk factors. However, high rates of pulmonary toxicity (24% of patients) and severe toxicity have been reported among older HL patients [24,31].

This study had several strengths that allowed for the investigation of pulmonary events among HL patients treated with bleomycin. The study included all newly diagnosed HL patients which limited the possibility of selection bias. All patients had DOD healthcare coverage across the US along with complete health data capture regardless of the location of care (military facility or TRICARE network) so lost to follow-up was minimized. Also, the DOD population is similar in age and race composition as the general US population. However, there are study limitations that should be considered. Some patients opted to not have their oncology treatment covered by the DOD and sought private pay care; however, this was a small proportion (10%) of the study population. Even though the DOD population is similar in age and race as the US population, the study findings may not be generalizable to all HL patients. The statistical models could only include the characteristics available in the EMR or tumor registry so other factors not included in the models may predict pulmonary events in bleomycin-treated HL patients.

Conclusion

A significant proportion of HL patients (all stages and stages 3-4) still experience pulmonary events long after treatment with bleomycin. The occurrence of pulmonary events may cause long-term decrements in health and quality of life for survivors of HL, especially given the highly curable nature of HL. Bleomycin-associated pulmonary events could not be predicted using models with demographic and clinical characteristics, making it difficult to identify patients likely to experience pulmonary events before the start of combination chemotherapy. Clinicians need to proactively discuss the risks with their patients.

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Research Disclaimer

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Conflict of Interest

This research was supported by Seattle Genetics, Inc. Ms. Evans is an employee of Health ResearchTx LLC, which has a business relationship with Seattle Genetics, Inc. CDR Morris reports no conflicts of interest.

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