Published in final edited form as:

Leuk Lymphoma. 2012 June ; 53(6): 1130–1136. doi:10.3109/10428194.2011.645208.

Risk factors for development of pneumonitis after high-dose chemotherapy with cyclophosphamide, BCNU, and etoposide (CBV) followed by autologous stem cell transplant

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Abstract

Pneumonitis is a complication of high-dose chemotherapy and autologous stem cell transplantation (HDC-ASCT) regimens containing BCNU. Our goal was to define the incidence and risk factors for pneumonitis in lymphoma patients receiving a uniform conditioning regimen in the modern era. We studied 222 patients who received HDC-ASCT using cyclophosphamide, BCNU, and VP-16 (CBV). Pneumonitis incidence was 22%, with 19% receiving systemic corticosteroid treatment, and 8% requiring inpatient hospitalization for pneumonitis. Three patients died secondary to pneumonitis-related complications. The following variables were independently associated with pneumonitis: prior mediastinal radiation (odds ratio 6.5, 95%CI 2.3–18.9, $P=0.0005$), total BCNU dose above 1000 mg (OR 3.4, 95%CI 1.3–8.7, $P=0.012$), and age less than 54 (OR 3.0, 95%CI 1.4–6.5, $P=0.0037$). Increased vigilance for symptoms of pneumonitis is warranted for patients with prior mediastinal radiation and for younger patients, and dose reduction may be considered for patients who would receive greater than 1000 mg of BCNU.

Introduction

High-dose chemotherapy followed by autologous stem cell rescue, or autologous stem cell transplantation (ASCT), remains an important treatment for certain hematologic malignancies. ASCT is effective in relapsed and refractory Hodgkin and non-Hodgkin lymphomas [1, 2], and over 30,000 autologous transplants are performed yearly worldwide [3]. Several chemotherapy preparative regimens are used in ASCT, and component agents are chosen because of activity against particular lymphoma subtypes; however, there has not been a randomized clinical trial to support the superiority of one regimen over another.

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This work was presented in part at the 52nd Annual Meeting of the American Society of Hematology, December 3–7, 2010, Orlando, FL.

Potential Conflicts of Interest

YC has received grant support from Otsuka Pharmaceuticals, Inc.; Millennium Pharmaceuticals, Inc.; and Bayer/Onyx Pharmaceuticals. The remaining authors have no conflicts of interest to disclose.

Therefore, regimens are chosen by institutional preference and experience, and by considering each regimen's potential toxicities. In many institutions, including our own, the CBV regimen (cyclophosphamide, BCNU, and etoposide [VP-16]) is the standard ASCT preparative regimen for patients with lymphoma.

Acute onset interstitial pneumonitis is a recognized complication of high-dose chemotherapy regimens containing BCNU [4]. Early dose-finding trials of the CBV regimen noted an elevated frequency of pneumonitis with increasing BCNU dose by body surface area [5]. This observation has been confirmed in larger series [6, 7]. However, based on these studies, the 450 mg/m² total BCNU dose used in our current CBV regimen is thought to minimize lung toxicity. In most cases, BCNU-associated pneumonitis is highly responsive to prompt initiation of systemic corticosteroid therapy, but can be a cause of transplant-related mortality if untreated, or in rare cases that are refractory to steroid treatment.

Most of the published series evaluating pneumonitis after BCNU-containing HDC-ASCT regimens either describe small groups of heterogeneously-treated lymphoma patients, or are larger cohorts of solid tumor patients treated with ASCT [8–15]. There are conflicting data as to the significance of pre-transplant risk factors for developing pneumonitis, including whether prior radiotherapy influences risk. Furthermore, it is not clear if modern agents used in lymphoma treatment prior to transplant (e.g., rituximab and gemcitabine, among others) affect pneumonitis risk. Therefore, we designed this study to retrospectively determine the incidence of pneumonitis associated with the CBV regimen in a large series of lymphoma patients receiving a uniform conditioning regimen in the current era. We also investigated pre-transplant patient characteristics for any statistical associations with the development of pneumonitis.

Methods

Patients

Medical records were reviewed from 222 consecutive patients treated during the period of September 11, 2007 through September 15, 2009 at the Dana-Farber Cancer Institute (DFCI) and the Massachusetts General Hospital Cancer Center (MGHCC), who received high-dose chemotherapy with cyclophosphamide, BCNU (carmustine), and VP-16 (etoposide), followed by autologous stem cell rescue (ASCT) for lymphoma. This study was approved by the Institutional Review Board of the Dana-Farber/Harvard Cancer Center. Disease stage at diagnosis was determined by the Ann Arbor staging system. Response evaluation prior to ASCT was determined by PET and CT scans. Overall survival (OS) was defined as the time from transplantation until death from any cause. Progression-free survival (PFS) was defined as the time from transplantation until disease relapse or death from any cause.

Treatment protocol

Beginning on day 6 prior to infusion of stem cells, patients received cyclophosphamide 750 mg/m² IV every 12 hours for four days (total dose 6000 mg/m²), BCNU 112.5 mg/m² IV daily for four days (total dose 450 mg/m²), and VP-16 (etoposide) 200 mg/m² IV every 12 hours for four days (total dose 1600 mg/m²). MESNA was given as a continuous infusion of 750 mg/m² per day for five days, beginning 30 minutes prior to the first dose of cyclophosphamide. For patients treated at MGHCC (29 of 222 patients) who weighed more than 20% above ideal body weight, the doses of cyclophosphamide, BCNU, etoposide, and MESNA were adjusted to the mean of actual and ideal body weight. DFCI patients were dosed based on actual body weight. On the day of transplantation, patients received autologous peripheral blood stem cells (except for three patients who received autologous

bone marrow, and two who received peripheral blood stem cells plus bone marrow) at a target dose of $>2 \times 10^6$ CD34⁺ cells/kg. All patients received filgrastim (G-CSF) at 5 µg/kg intravenously or subcutaneously daily starting on day 5 after transplant, continuing until absolute neutrophil count (ANC) was greater than 1000/µl on two consecutive days. Patients remained hospitalized until neutrophil engraftment, defined as ANC $>500/\mu\text{l}$ on two consecutive days.

Data collected and definition of pneumonitis

Records were retrospectively reviewed for pre-transplant characteristics that we hypothesized might be related to the incidence of pneumonitis. Prior radiation therapy was classified as “thoracic” when directed to any portion of the thorax including the mediastinum, or as “mediastinal”, when only the mediastinal field was irradiated. Pneumonitis was defined retrospectively and clinically as follows. All patients were required to be symptomatic (shortness of breath, dyspnea, and/or cough). Some patients with pneumonitis had fever, but fever alone was not sufficient to define pneumonitis in the absence of respiratory symptoms. All patients either demonstrated diffuse bilateral infiltrates on chest radiography (the vast majority of cases), or negative imaging without evidence of an alternative focal pulmonary process. Infectious studies were not required, however, those patients who demonstrated a documented infectious cause for their signs and symptoms (including sputum cultures, nasal swabs for respiratory virus analysis, and washings or biopsies from bronchoscopy) were not considered to have pneumonitis.

Statistical analyses

Kaplan-Meier estimation of OS and PFS were calculated with their corresponding 95% confidence intervals. Multivariable Cox regression models of OS and PFS were utilized to provide adjusted treatment comparisons and identify simultaneous significant prognostic factors. Final models for both OS and PFS were built using a stepwise selection method. For stepwise multivariable Cox regression analysis, a variable had to be significant at the 0.25 level to be entered into the model, and had to be significant at the 0.05 level to remain in the model. Categorical patient characteristics were compared between patients with and without pneumonitis using Chi-squared tests with a two-sided significance level of 0.05. Where event frequencies were small, Fisher’s exact tests were used. Continuous patient characteristics were compared between patients with and without pneumonitis using Kruskal-Wallis tests with a two-sided significance level of 0.05. The cumulative incidences of pneumonitis events and death due to any other cause were estimated in a competing risk model using the method of Gray [16]. To determine factors independently associated with pneumonitis, we performed a multivariable logistic regression analysis of pneumonitis or not within four months post-transplant; using a competing risk analysis we excluded patients without pneumonitis who experienced relapse, censoring, or death in that time period.

Results

Patients and survival

The characteristics of the 222 patients studied are shown in Table I. The median follow-up among all patients alive is 12 months (range 2.6–25.2). Overall survival (OS) at one year was 91.8% (95% CI, 87.7–95.9%), and progression-free survival (PFS) was 70.8% (95% CI, 64.3–77.4%; Figure 1A and Table II). There were no characteristics, including development of pneumonitis, associated with PFS on multivariable analysis. Only lack of CR or PR prior to ASCT was associated with inferior OS on multivariable Cox regression modeling (hazard ratio 0.2, 95% CI 0.05–0.72, $P=0.01$). There were four treatment-related deaths. Three deaths were related to pneumonitis, and occurred at 62, 67, and 149 days post-transplant. One death due to hepatic veno-occlusive disease occurred 27 days post-transplant.

Pneumonitis incidence and outcomes

The overall incidence of pneumonitis was 22.1%, occurring in 49 patients. One-, two-, and three-month cumulative incidences of pneumonitis (adjusted for competing mortality) were 2.7%, 15.7% and 21.6%, respectively. The median time to development of pneumonitis was 50 days (range 26–199 days), and 98% of cases (48 of 49) occurred within 91 days post-transplant (Figure 1B). 42 of 222 patients (18.9%) received systemic corticosteroid treatment for pneumonitis, and 18 of 222 (8.1%) were hospitalized due to pneumonitis. The diagnostic evaluation of pneumonitis differed based on patient presentation and clinician preference. 34 patients were evaluated with a chest CT scan, twelve patients had chest x-ray only. 40 cases had diffuse or patchy bilateral infiltrates; six patients had negative imaging on chest x-ray, but were treated without further evaluation due to highly suggestive presentations. Eight patients underwent bronchoscopy, and had negative bronchoalveolar lavage studies for one or more of: respiratory viruses, cytomegalovirus, varicella zoster virus, herpes simplex virus, *Legionella*, mycobacteria, *P. jiroveci*, *M. pneumoniae*, and fungi. Biopsies (performed in 7 patients) demonstrated diffuse alveolar damage, and/or organizing pneumonia with early fibrosing changes. Twenty-nine patients had repeat pulmonary function testing performed at the time of presentation with pneumonitis. The median decreases in percent predicted FEV1, FVC, and DLCO in patients with pneumonitis compared to pre-transplant values were 21%, 19%, and 31%, respectively.

Treatment for pneumonitis also varied based on physician practice. Five patients were not treated despite recognition of possible pneumonitis by their treating physician; their symptoms all resolved over 1–6 months. Patients who received corticosteroids were treated with oral prednisone at doses between 0.5 and 1 mg/kg daily for 2–8 weeks. Doses were tapered over 6–48 weeks, beginning when patients experienced symptomatic improvement, and where tested, as PFTs improved. Nine patients experienced relapse of symptoms during a taper or after discontinuation of steroids, and required retreatment with a more prolonged course before achieving clinical resolution of symptoms. Two of the three patients who died secondary to pneumonitis were placed on systemic corticosteroids immediately upon presentation with dyspnea 26 and 52 days after transplant. Both had minimal response to steroids and died after prolonged hospitalizations. The other pneumonitis-related death occurred in a 70-year-old woman with prior cardiac disease whose symptoms of dyspnea and hypoxia 48 days after transplant were initially attributed to congestive heart failure. However, despite eventual treatment with systemic corticosteroids, she experienced progressive respiratory failure over several weeks leading to her death.

Risk factor analysis

Univariable analysis was performed for pre-transplant factors hypothesized to have a possible association with the development of pneumonitis (Table III). Age, disease status at the time of ASCT, prior thoracic radiation, prior mediastinal radiation, and prior treatment with bleomycin, were found to be statistically significantly different between patients with and without pneumonitis at a $P < 0.05$ level. There was a trend toward an association between prior gemcitabine chemotherapy and pneumonitis ($P = 0.1$). Younger age was associated with development of pneumonitis when tested as a continuous variable, and as a dichotomous variable using the cohort median age of 54 as a cut-off. Gender, body mass index, history of smoking, diagnosis, disease stage at diagnosis, number of prior chemotherapy regimens, parenchymal lung involvement by lymphoma, pre-transplant pulmonary function testing results (examining FEV1, FVC, and DLCO as continuous variables), prior treatment with rituximab, and CD34⁺ cell dose received were not found to be statistically significantly different between patients who did and did not develop pneumonitis.

We next explored whether the dose of BCNU received correlated with the development of pneumonitis. Neither body mass index nor body surface area was associated with pneumonitis (Table III and data not shown). There was no difference in pneumonitis incidence between patients undergoing ASCT at MGH and DFCI ($P=0.33$), despite different protocols for dosing overweight and obese patients. However, because some providers had empirically reduced the body surface area-calculated BCNU dose for obese patients, we determined the rate of pneumonitis based on total dose of BCNU received. When patients were placed in groups based on dose, there appeared to be an increase in pneumonitis incidence in those patients who received 1000 mg or greater of BCNU (Figure 2). Accordingly, on univariable analysis, BCNU dose of 1000 mg was associated with a statistically significant higher rate of pneumonitis (Table III, $P=0.037$).

Multivariable logistic regression analysis was performed on the odds of developing pneumonitis in the first four months post-transplant, including the following variables: gender, age, BMI, diagnosis, history of smoking, stage at diagnosis, prior rituximab, prior bleomycin, prior gemcitabine, prior thoracic radiation, prior mediastinal radiation, disease status at ASCT, and BCNU dose. Thirty-one patients without pneumonitis who had death, relapse, or censoring in the first four months post-transplant were excluded. Prior mediastinal radiation therapy, BCNU dose greater than or equal to 1000 mg, and age less than 54 were each independently associated with development of pneumonitis at a $P<0.05$ level (Table IV).

Discussion

We have shown that pneumonitis is a significant cause of post-transplant morbidity after ASCT in lymphoma patients using the CBV regimen, occurring in 22% of patients in this cohort. Three of four instances of treatment-related mortality were related to pneumonitis. A multivariable analysis identified three factors as independently associated with development of pneumonitis: prior mediastinal radiation therapy, total BCNU dose received of greater than 1000 mg, and younger age.

The published risk of pneumonitis after ASCT using BCNU ranges from 4–59%, although prior studies used widely varying doses and schedules of BCNU as part of different high-dose chemotherapy combinations, included patients with many tumor types and prior therapies, and used variable definitions of pneumonitis [4, 8–15]. The data presented here define the incidence of pneumonitis after CBV ASCT in lymphoma patients in the modern era. These findings establish that prior mediastinal radiation therapy is a risk factor for development of post-transplant pneumonitis. It is not clear why younger age is associated with higher risk of pneumonitis. This could be related to true biological differences in younger patients (e.g., differential drug metabolism, hormonal factors, or heightened inflammatory response), or an as yet unidentified confounding factor that was not collected in our analysis. Study of a larger multicenter population of CBV ASCT, and/or inclusion of patients who received other common BCNU-containing regimens such as BEAM (BCNU, etoposide, cytarabine, and melphalan) may help confirm and expand these findings. We have initiated such a project in collaboration with the Center for International Blood and Marrow Transplant Research (CIBMTR).

Several previous studies have determined that the risk of pulmonary complications increases with higher body surface area-based (mg/m^2) dosing of BCNU [5–7, 17]. We additionally find here that the total dose of BCNU received is associated with pneumonitis, even in a cohort treated with a fixed dose per body surface area. The suggestion of a threshold effect for increasing toxicity at total doses of greater than 1000 mg suggests that overweight and obese patients may be at higher risk. Body mass index and body surface area were not

associated with pneumonitis in this study, presumably due to the fact that some providers had empirically dose-reduced their obese patients (15 patients [7%]) and therefore they did not receive the full 450 mg/m² of BCNU. A dose threshold above which toxicity increases is similar in concept to that seen with other chemotherapy agents such as anthracyclines [18]. If these data are corroborated in larger data sets, and potentially with other BCNU-containing regimens, there may be justification for dose reduction or capping the total BCNU dose.

This study is limited by its retrospective nature, and particularly by the retrospective method of determining which patients developed pneumonitis. However, given that there is near concordance between the incidence of pneumonitis as defined in this study (22.1%), and the percentage of patients who were treated with corticosteroids (18.9%), the retrospective assignment as to whether a patient developed pneumonitis therefore parallels the clinical judgment of the treating physicians. Some patients were treated empirically with broad-spectrum antibiotics in addition to corticosteroids, and therefore there may have been patients with respiratory infections who had false negative or incomplete infectious evaluations. The observation that many of the patients had rapid improvement of their symptoms with corticosteroid therapy, however, also corroborates the retrospective definition of pneumonitis for the purposes of this study.

These data do not conclusively identify BCNU as the causative agent of pneumonitis, although the observed dose threshold supports the hypothesis. There are data suggesting that treatment with BCNU in combination with cyclophosphamide may particularly enhance the likelihood of pulmonary toxicity [4, 19]. Similarly, it is possible that another concomitantly delivered medication or concurrent infection is responsible for, or increases the risk of developing pneumonitis. BCNU area-under-the-curve (AUC) measurements correlate with pulmonary side-effects in pharmacokinetic studies [20]. It is possible that AUC-adjusted therapy might optimize anti-lymphoma activity while reducing the risk of pulmonary toxicity. An analogous balance between efficacy and toxicity was observed with busulfan pharmacokinetics in preparative regimens prior to stem cell transplantation [21].

A previous study showed that preemptive therapy with steroids in asymptomatic patients with a decrease in DLCO post-transplant did not reduce the risk of developing subsequent pulmonary toxicity [22]. Understanding which patients are at highest risk of pneumonitis may allow targeting those at highest risk for preventative measures. At present, the most important intervention for avoiding morbidity and mortality associated with pneumonitis is clinical awareness and prompt initiation of systemic corticosteroids. The vast majority of patients with pneumonitis in this cohort had significant improvement in relatively short periods of time on steroid therapy. However, there were some patients who required a more prolonged course and had relapse of symptoms when steroids were tapered. It is unclear how to differentiate, a priori, between the rapid and delayed responders, or how to predict those who may be refractory to initial treatment and/or die as a result of pneumonitis. Furthermore, since some patients are discharged from the care of a transplant center while still in a window of risk for pneumonitis, it remains imperative that local oncologists and primary care physicians continue to monitor patients for signs and symptoms of pulmonary toxicity. The total incidence of pneumonitis, particularly late occurrences, may be underestimated because the median follow-up in this cohort was only 12 months, providing rationale for longer-term study of this cohort and in the CIBMTR analysis described above.

The pathophysiologic mechanism of BCNU-associated pulmonary toxicity is not entirely clear. Oxidative stress and glutathione dysfunction, as well as immune-mediated injury have been implicated as causative factors and potential targets for prophylaxis and therapy.[14, 23, 24] The delayed presentation after transplant may be consistent with initial tissue injury

followed by pneumonitis progression at the time of lymphocyte recovery. Further basic investigation to delineate the contribution of each mechanistic factor may be helpful in improving patient outcomes using rationally-designed treatments.

There are data to suggest that toxicity related to some chemotherapy, particularly targeted agents, may actually correlate with improved tumor response. For example, rash with cetuximab [25] and hypertension with bevacizumab [26] are associated with improved survival. There are less clear data for correlation between toxicity and efficacy for conventional chemotherapeutics (e.g., irinotecan and UGT1A1 polymorphisms [27]). In our study, there was no correlation between development of pneumonitis and progression-free or overall survival, but the relatively short follow-up precludes a comprehensive analysis of survival. It will be important to assess survival in any cohort of patients where a BCNU dose reduction or cap is employed, to ensure that there is no negative impact on anti-lymphoma activity. Additionally, we may be able to revisit our cohort in the future to more definitively determine if pneumonitis is associated with any change in survival.

In summary, we have found that the risk of pneumonitis after CBV ASCT in a large cohort of lymphoma patients is 22%, and that prior mediastinal radiation therapy, total dose of BCNU received above 1000 mg, and younger age are correlated with the development of pneumonitis. Since ASCT remains an important component of therapy for lymphoma, and in the absence of obvious clinical superiority of one regimen over another, further study is warranted to validate these risk factors to continue to improve outcomes after autologous transplantation.

Acknowledgments

The authors thank Joseph Antin and Janet Murphy for helpful discussions.

YC is a recipient of a career development award from the Leukemia & Lymphoma Society. Additional support provided by NIH T32 CA071345 (AAL).

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Figure 1. Kaplan-Meier estimates of survival and development of pneumonitis
 (A) Overall (black solid line) and progression-free (gray dashed) survival probabilities after transplant as calculated by the Kaplan-Meier method are shown. (B) Cumulative probability of pneumonitis (black solid) and transplant-related mortality (gray dashed) over time post-transplant are shown. Censored subjects are represented by vertical marks.

Figure 2. Incidence of pneumonitis relative to total BCNU dose

Patients were divided into eight groups based on total BCNU dose received. The percentage of patients in each group that developed pneumonitis is shown in the graph. Numbers above each bar represent the absolute number of patients with pneumonitis and the total number of patients in each group.

Table I

Characteristics of patients.

Parameter	Number (%)
Total patients	222
Age, median (range)	54 (21–77)
Male	136 (61.3)
Female	86 (38.7)
Hodgkin lymphoma	65 (29.3)
Non-Hodgkin lymphoma	157 (70.7)
DLBCL	85 (38.3)
MCL	28 (12.6)
FL	23 (10.4)
T NHL	16 (7.2)
PCNSL	2 (0.9)
LPL	2 (0.9)
Burkitt lymphoma	1 (0.5)
Disease status at transplant	
CR	142 (64)
PR	70 (31.5)
PD/refractory	10 (4.5)
Prior chemotherapy regimens	
1	37 (16.7)
2	118 (53.2)
3	50 (22.5)
4 or more	17 (7.7)
History of smoking	96 (43.2)
Mediastinal disease involvement	158 (71.2)
Prior thoracic RT	41 (18.5)
Prior mediastinal RT	24 (10.8)
Prior bleomycin	68 (30.6)
Prior gemcitabine	26 (11.7)
Prior rituximab	145 (65.3)
Pulmonary involvement by lymphoma	12 (5.4)
Pre-transplant FEV1 [median (range)]	98 (47–142)
FVC	95 (53–132)
D _L CO	87 (49–127)

DLBCL, diffuse large B cell lymphoma; MCL, mantle cell lymphoma; FL, follicular lymphoma; T NHL, T cell non-Hodgkin lymphoma; PCNSL, primary central nervous system lymphoma; LPL, lymphoplasmacytic lymphoma; CR, complete response; PR, partial response; PD, progressive disease; RT, radiation therapy; FEV1, forced expiratory volume in one second (% predicted); FVC, forced vital capacity (% predicted); D_LCO, diffusing capacity for carbon monoxide (% predicted, corrected for hemoglobin)

Table II

Patient outcomes.

12 month outcome	
Overall survival [probability (95% CI)]	91.8% (87.7 – 95.9)
Progression-free survival [probability (95% CI)]	70.8% (64.3 – 77.4)
Non-relapse mortality [n (%)]	4 (1.8)
Pneumonitis	3
Hepatic veno-occlusive disease (VOD)	1
Pneumonitis [n (%)]	49 (22.1%)
Steroid treatment for pneumonitis	41 (18.5%)
Hospitalization for pneumonitis	18 (8.1%)
Time to pneumonitis, days [median (range)]	50 (26–199)

95% CI, 95% confidence interval

Table III

Univariable analysis for association with pneumonitis.

	Pneumonitis			P-value
	Total (n=222)	Yes (n=49)	No (n=173)	
Sex [n (%)]				
Male	136 (61.3)	28 (57.1)	108 (62.4)	0.5026 (P)
Female	86 (38.7)	21 (42.9)	65 (37.6)	
Age				
Median	54	46	56	0.0110 (K)
Min	21	22	21	
Max	77	72	77	
Age [n (%)]				
< 54	107 (48.2)	34 (69.4)	73 (42.2)	0.0008 (P)
54	115 (51.8)	15 (30.6)	100 (57.8)	
BMI [n (%)]				
< 30	138 (62.2)	26 (53.1)	112 (64.7)	0.1367 (P)
30	84 (37.8)	23 (46.9)	61 (35.3)	
BMI				
Median	28	29	28	0.3415 (K)
Min	16.9	19.5	16.9	
Max	49.5	48.0	49.5	
BCNU dose [n (%)]				
< 1000 mg	197 (88.7)	39 (79.6)	158 (91.3)	0.0371 (F)
1000 mg	25 (11.3)	10 (20.4)	15 (8.7)	
History of smoking [n (%)]				
Yes	96 (43.2)	18 (36.7)	78 (45.1)	0.2975 (P)
No	126 (56.8)	31 (63.3)	95 (54.9)	
Status at ASCT [n (%)]				
CR	142 (64.0)	25 (51.0)	117 (67.6)	0.0327 (E)
PR	70 (31.5)	23 (46.9)	47 (27.2)	
PD/refractory	10 (4.5)	1 (2.0)	9 (5.2)	
Prior thoracic RT [n (%)]				
Yes	41 (18.5)	14 (28.6)	27 (15.6)	0.0390 (P)
No	181 (81.5)	35 (71.4)	146 (84.4)	
Prior mediastinal RT [n (%)]				
Yes	24 (10.8)	12 (24.5)	12 (6.9)	0.0005 (P)
No	198 (89.2)	37 (75.5)	161 (93.1)	

	Pneumonitis			P-value
	Total (n=222)	Yes (n=49)	No (n=173)	
Prior bleomycin [n (%)]				
Yes	68 (30.6)	23 (46.9)	45 (26.0)	0.0050 (P)
No	154 (69.4)	26 (53.1)	128 (74.0)	
Prior gemcitabine [n (%)]				
Yes	26 (11.7)	9 (18.4)	17 (9.8)	0.1007 (P)
No	196 (88.3)	40 (81.6)	156 (90.2)	
Prior rituximab [n (%)]				
Yes	145 (65.3)	27 (55.1)	118 (68.2)	0.0888 (P)
No	77 (34.7)	22 (44.9)	55 (31.8)	
Pulmonary involvement by lymphoma [n (%)]				
Yes	12 (5.4)	4 (8.2)	8 (4.6)	0.31 (P)
No	210 (94.6)	45 (91.8)	165 (95.4)	

P, Pearson's Chi-Square Test; E, Exact Test for RxC Tables; K, Kruskal-Wallis Test; F, Fisher's Exact Test; StdDev, standard deviation; BMI, body mass index; ASCT, autologous stem cell transplant; CR, complete response; PR, partial response; PD, progressive disease; RT, radiation therapy

Table IV

Multivariable logistic regression model for factors independently associated with pneumonitis.

	Odds Ratio Estimate	Lower 95% Confidence Limit for Odds Ratio	Upper 95% Confidence Limit for Odds Ratio	P-value
Prior mediastinal RT	6.5	2.3	18.9	0.0005
BCNU dose 1000 mg	3.4	1.3	8.7	0.0120
Age < 54	3.0	1.4	6.5	0.0037

RT, radiation therapy