Published in final edited form as:

Clin Lymphoma Myeloma Leuk. 2012 October ; 12(5): 325–329. doi:10.1016/j.clml.2012.06.002.

Chemotherapeutic Agents Increase the Risk for Pulmonary Function Test Abnormalities in Patients With Multiple Myeloma

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Abstract

Case reports of pulmonary toxicity have been published regarding bortezomib, lenalidomide, and thalidomide but there are no published reports looking at the possible long-term pulmonary effects of these medications. This article describes a possible relationship between the administration of bortezomib and thalidomide and the development of pulmonary function test (PFT) abnormalities. It also suggests that routine pulmonary function testing may be required in patients receiving these medications until larger studies can be performed to confirm this observation.

Background—Multiple myeloma is a common malignancy accounting for approximately 1% of all malignancies worldwide. Bortezomib, lenalidomide, and thalidomide are immunomodulatory derivatives that are used in the treatment of multiple myeloma (MM). There have been case reports of pulmonary disease associated with these agents, but the effect of these agents on pulmonary function test (PFT) results is unknown.

Patients and Methods—We reviewed the records of 343 patients with MM who underwent PFTs before autologous stem cell transplantation. One hundred nine patients had not received any of the 3 medications, whereas 234 had received 1 or more of these agents.

Results—Patients exposed to bortezomib were more likely to have obstructive PFT results ($P = .015$) when compared with patients not exposed to this medication. Restrictive PFT results were more likely after exposure to thalidomide ($P = .017$). A logistic regression model was performed and when adjusted for age, sex, Durie-Salmon (DS) stage, body mass index (BMI), time from diagnosis to transplantation in days, and smoking history, the odds of obstruction were 1.96 times higher for patients who received bortezomib. The odds of restriction were 1.97 times higher after exposure to thalidomide.

Conclusion—There appears to be a risk of PFT abnormalities developing in patients treated with bortezomib and thalidomide.

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Disclosure

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

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Keywords

Airflow obstruction; Bortezomib; Lenalidomide; Multiple myeloma; Pulmonary function tests; Thalidomide

Introduction

Multiple myeloma (MM) is a mature B-cell malignancy with a plasma cell phenotype characterized by lytic bone lesions (60%), renal insufficiency (20%–50%), anemia (70%), hypercalcemia (15%), and immunodeficiency. The most common presenting symptoms are fatigue, bone pain/fracture, and renal insufficiency related to the underlying malignant clone, and therapy is required immediately.¹

Over the past decade, the survival of patients with newly diagnosed MM, particularly those younger than 60 years, has significantly improved.² The widespread use of autologous hematopoietic stem cell transplantation (HSCT) and the introduction into clinical practice of the proteasome inhibitor bortezomib and the immunomodulatory derivatives thalidomide and lenalidomide^{3–5} have significantly contributed to major advances in MM therapy and prognosis.⁶ HSCT is considered the standard of care for younger patients with newly diagnosed MM based on the increased rate of complete response and prolonged overall survival compared with conventional chemotherapy in several randomized studies.^{7,8} Thalidomide, lenalidomide, and bortezomib are given together along with dexamethasone or they are given sequentially in fit patients before autologous transplantation to reduce disease burden.

Multiple side effects have been associated with the aforementioned chemotherapeutic agents. Case reports of adverse pulmonary effects associated with thalidomide are numerous. Some of the described effects include organizing pneumonia and pulmonary hypertension.^{9,10} Hypersensitivity pneumonitis and interstitial pulmonary disease have been described after administration of lenalidomide.^{11,12} Finally, bortezomib administration was associated with acute respiratory insufficiency and wheezing in a case series from a single institution.¹³ At this time there are no available data describing the subacute to long-term pulmonary effects of these medications or findings on pulmonary function tests (PFTs).

We reviewed PFT results performed as part of the eligibility workup before autologous HSCT to determine if these medications are associated with adverse pulmonary effects.

Material and Methods

We reviewed the records of patients with MM who underwent autologous stem cell transplantation at the James Cancer Hospital at the Ohio State University from January 1, 2000 through May 30, 2010. The study was approved by the Institutional Review Board of the Ohio State University. We grouped patients by treatment with bortezomib, lenalidomide, or thalidomide, and those with no exposure to these medications before transplantation. The PFT values included spirometry, lung volumes, and diffusing capacity of lung for carbon monoxide. The Fisher exact method was used to ascertain if there was an association between bortezomib, lenalidomide, or thalidomide and pulmonary complications (restriction or obstruction). Obstruction is defined as the actual forced expiratory volume in 1 second (FEV₁)/forced vital capacity (FVC) ratio less than the lower 95% confidence interval (CI) of FEV₁/FVC, and restriction is defined as actual total lung capacity (TLC) < 95% CI of TLC as recommended by the American Thoracic Society.¹⁴ Logistic regression models were used to estimate the odds of either obstruction or restriction developing based on whether the patient received or did not receive bortezomib, lenalidomide, or thalidomide. Results are

adjusted for smoking history (pack-years), age, sex, body mass index (BMI), Durie-Salmon (DS) stage (1, 2, or 3), and time between diagnosis and transplantation (days). All analyses were run using Stata 10.2 or 11.1 (Stata Corp, College Station, TX).

Results

A total of 360 patients were identified, of which 343 had complete pretransplantation PFT results and medication histories available. A summary of patient demographics is provided in Table 1. Of all pretransplantation PFTs performed, 47 (13.7%) patients demonstrated obstructive PFTs and 76 (22.1%) demonstrated restrictive findings on PFT results. A summary of the medication distribution is listed in Table 2. Of the 343 patients, 109 did not have exposure to any of the 3 medications. Of these patients, almost all (107 of the 109) had VAD (vincristine, doxorubicin, and dexamethasone) or DVD (pegylated liposomal doxorubicin, vincristine, and dexamethasone) as the primary treatment regimen. We looked at the incidence of obstruction and restriction in patients who had ever had 1 of the 3 medications (bortezomib, lenalidomide, or thalidomide) in their treatment regimen. Twenty-six of 131 (19.8%) patients with a bortezomib-containing regimen experienced obstruction as compared with 21 of 212 (9.9%) patients without exposure to bortezomib ($P=.015$) (Figure 1A). Obstruction was not more common in patients who had been exposed to lenalidomide or thalidomide. Thalidomide was the only agent associated with restriction (Figure 1B). One hundred nine patients received a thalidomide-containing regimen and 33 (30.3%) demonstrated restriction on PFT results compared with 43 of 234 (18.4%) patients who never received thalidomide ($P=.017$). Because many factors may affect PFT results, a logistic regression model was performed adjusting for smoking history (pack-years), age, sex, DS stage, BMI, and time between diagnosis and transplantation. Adjusted results included only 330 patients because 13 patients did not have DS stage available. The adjusted odds of obstruction were 1.96 times higher (95% CI, 1.01–3.79; $P=.047$) after exposure to bortezomib, and the adjusted odds of restriction were 1.97 times higher (95% CI, 1.13–3.44; $P=.017$) after exposure to thalidomide (Table 3).

The various combinations of medications were analyzed, including bortezomib and lenalidomide, bortezomib and thalidomide, lenalidomide and thalidomide, and the combination of all 3 medications. The combination of bortezomib and lenalidomide produced a high percentage of obstruction; however, when analyzed in the adjusted logistic regression equation it was not significant. The adjusted odds of obstruction were 2.01 times higher (95% CI, 0.87–4.64; $P=.101$).

Other medications could affect pulmonary function, such as dexamethasone; however, most patients had dexamethasone in their treatment regimen (>95% of the entire study population), so it was not included in the regression model. Another factor that could affect pulmonary function is the incidence of compression fractures and bone health. Although we do not have the exact number of compression fractures, the percentage of patients receiving zoledronic acid or pamidronate was 97 of 343 (28.3%) of the entire population. The percentage of patients who had radiation therapy to a bone lesion was 91 of 343 patients (26.5%) and was very similar between groups.

Discussion

We describe a 2-fold increased odds of PFT abnormalities with novel agents when used before transplantation— obstruction for bortezomib-exposed patients and restriction for thalidomide-exposed patients. Data from other cancers show that alkylator-based chemotherapy,^{15–17} with or without radiation therapy,^{18,19} transiently decreases primarily diffusion of carbon monoxide; for neoadjuvant chemotherapy, this is associated with

operative complications.²⁰ Based on data from allogeneic transplant procedures, total body irradiation (TBI) affects pulmonary function in all patients, even if the total dose is only 2 Gy.²¹ TBI affects nearly all parameters on PFTs, which eventually normalize in adults²² but not in some children.²³

Bortezomib, lenalidomide, and thalidomide have been associated with several pulmonary complications, although to our knowledge they have not been associated with obstructive or restrictive PFT results before. Rates of reported adverse pulmonary complications are low for all 3 medications. There were no pulmonary side effects reported by 10% or more of the patients administered bortezomib in a phase II trial of the medication.²⁴ A grade 4 adverse pulmonary effect (dyspnea) was reported in 1.7% of patients who received lenalidomide.²⁵ The pulmonary side effects of bortezomib specifically have been reviewed in a case series at a single institution.¹³ These patients presented with asthma-like symptoms that progressed to respiratory failure, which responded to steroids, presumably a pneumonitis rather than a gradually developing obstructive abnormality as we saw in our population.

The mechanism of pulmonary injury caused by these medications is unclear. Bortezomib acts through proteasome inhibition, which results in a complex change in regulatory proteins, transcription factors, and oncogenes.²⁶ These changes may over time lead to a remodeling of the small airways in the pulmonary parenchyma. Thalidomide is known to have some pulmonary side effects based on previous case reports. Organizing pneumonia and hypersensitivity pneumonitis may be associated with restrictive PFT results, although we are not aware of any studies to measure pulmonary function in patients before and after receiving thalidomide.^{9,12}

There are several limitations in a retrospective study of this nature, and our findings require a larger prospective study to determine causality. Many patients had more than 1 of the 3 agents in their treatment regimen, and PFT results were not assessed after each agent was added or after a medication change. It should be noted that all PFT results were obtained before autologous stem cell transplantation, so the conditioning regimen was not a confounder. In addition we do not have information on previous pulmonary disease or pulmonary pathologic processes, which certainly could have an effect on the results.

If these findings are replicated in a larger prospective study, additional issues that will need to be addressed include whether PFT abnormalities correlate with symptoms. Additionally, it would be essential to know if airflow obstruction is reversible on medication discontinuation or if it is treatable with pulmonary medications such as inhaled corticosteroids. This is an important issue because abnormal pulmonary function testing, specifically a low FEV1 or DLCO, may affect eligibility for transplantation. Additionally, for those with restrictive disease, it would need to be determined if the restriction is from intrinsic pulmonary disease such as fibrosis or whether it reflects extrinsic disease such as muscle weakness of kyphoscoliosis from compression fractures.

Conclusion

In conclusion, we demonstrate increased odds of obstructive PFT abnormalities with bortezomib exposure, as well as increased odds of restrictive defects with thalidomide exposure. Our data suggest that clinicians should have a low threshold of suspicion for pulmonary abnormalities in patients exposed to bortezomib and thalidomide. It may be prudent to monitor PFTs before and after exposure to these medications until larger studies can be performed to confirm this observation.

Acknowledgments

This work was supported by a grant from the NIH (K08 HL080701) and therefore in accordance with their public access policy, the work is required to be placed in PubMed, Central upon acceptance. The content is solely the responsibility of the authors and does not represent the official views of the National Institutes of Health.

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Clinical Practice Points

- Bortezomib, lenalidomide, and thalidomide are immunomodulatory derivatives that are used in the treatment of multiple myeloma.
- Case reports of pulmonary toxicity have been published regarding these 3 agents, but there are no published reports looking at the possible long-term pulmonary effects of these medications.
- This article describes a possible relationship between the administration of bortezomib and obstructive pulmonary disease and the administration of thalidomide and the development of restrictive pulmonary disease.
- These findings suggest that routine PFT monitoring may be required in patients receiving these medications until larger studies can be performed to confirm this observation.

Figure 1.

Incidence of Obstruction and Restriction on Pretransplantation Pulmonary Function Tests (PFTs) in Patients Who Had Been Exposed to Bortezomib, Lenalidomide, or Thalidomide. (A) Obstruction was Seen in 26 of 131 Patients (19.8%) Exposed to Bortezomib Compared With 21 of 212 (9.9%) Patients Without Exposure to Bortezomib ($P = .015$). (B) Thirty-Three of 109 Patients (30.3%) Exposed to Thalidomide Showed Restrictive PFT Results Compared with 43 of 234 (18.4%) Patients Who Had Never Received Thalidomide ($P = .017$)

Table 1

Multiple Myeloma Patient Demographics

Demographics	All Patients
Number	343
Male	203
Female	142
Age, mean (SD)	56.2 (8.9%)
BMI, mean (SD)	30.3 (9.3%)
Conditioning, %	
BUCY/BUCYVP	16 (4.4%)
MEL/TBIMEL	329 (95.9%)
Durie-Salmon Stage 1	42 (12%)
Durie-Salmon Stage 2	53 (15%)
Durie-Salmon Stage 3	236 (68%)
Smoking History	130 (37%)
Pack years — median	30
Time from Diagnosis to BMT, median, d	340

Abbreviations: BMI =body mass index; BMT =bone marrow transplantation; BUCY/BUCYVP = busulfan, cyclophosphamide/busulfan cyclophosphamide, VP-16; MEL/TBIMEL = melphalan/ total body irradiation plus melphalan.

Table 2

Distribution of Medications

Combination of Drugs	Frequency	Percent
Other Treatment Regimens	109	31.8
Bortezomib Only	53	15.4
Lenalidomide Only	32	9.3
Thalidomide Only	62	18.0
Bortezomib and Lenalidomide Only	40	11.7
Bortezomib and Thalidomide Only	31	9.0
Lenalidomide and Thalidomide Only	9	2.6
Bortezomib, Lenalidomide, and Thalidomide	7	2.0
Total	343	100.0

Table 3
Logistic Regression Model in a Pretransplantation Multiple Myeloma Population [N = 343]

Outcome	Drug	Unadjusted Results (N = 343)			Adjusted Results (n = 330)		
		OR	95% CI	P Value	OR	95% CI	P Value
Obstruction	Bortezomib	1.68	0.91 3.08	.096	1.96	1.01 3.79	.047
Restriction	Bortezomib	0.74	0.43 1.27	.282	0.65	0.37 1.15	.140
Obstruction	Lenalidomide	0.82	0.40 1.68	.579	0.89	0.42 1.90	.762
Restriction	Lenalidomide	0.65	0.35 1.22	.183	0.68	0.36 1.29	.235
Obstruction	Thalidomide	0.84	0.43 1.63	.603	0.92	0.45 1.89	.823
Restriction	Thalidomide	1.93	1.14 3.26	.014	1.97	1.13 3.44	.017

Abbreviations: CI = confidence interval; OR = odds ratio.