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Use and Impact of Herpes Zoster Prophylaxis in Myeloma Patients Treated with Proteasome Inhibitors

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Among infections myeloma patients acquire, herpes zoster (shingles), due to reactivation of varicella zoster virus, is common^{1,2}. Increased susceptibility to zoster has been linked to proteasome inhibitors, especially bortezomib^{3,4}. Phase II and III studies of bortezomib-based therapies for myeloma have consistently noted a higher incidence of zoster^{4–8}. Consequently, zoster prophylaxis is recommended for patients on proteasome inhibitor therapy by guidelines^{9,10}. In this study, we assessed the use and adherence to zoster prophylaxis in myeloma patients on proteasome inhibitors.

We performed a retrospective cohort study utilizing the Truven MarketScan Commercial Claims and Encounters Database between January 1, 2009 and December 31, 2013. Individuals 18 years and older with myeloma (International Classification of Diseases, 9th Revision (ICD-9) code 203.0×) were identified. All were required to have received bortezomib and/or carfilzomib (identified using Healthcare Common Procedure Coding System (HCPCS) codes J9041, J9047, C9295) continuously for 3 months. We examined the subset of patients who took proteasome inhibitors 6 months as a sensitivity analysis. The index date was the date of first proteasome inhibitor use. Patients were followed from the first to last proteasome inhibitor use, end of enrollment from MarketScan, or 12/31/2013, whichever was earliest.

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Multiple covariates were entered in the models to identify predictors for use and adherence. These included age at index, geographic region, residence in a metropolitan statistical area, place of service for the initial patient encounter, employment status, health plan, type of pharmacy, and calendar year at index. The number of concurrent chemotherapy agents given, not including steroids, was assessed to determine whether use of more agents affects use of antiviral prophylaxis. Patients with a history of herpes infection or who were on antiviral therapy prior to first proteasome inhibitor use were included. Comorbidity was defined using the Deyo classification of the Charlson comorbidity score (0, 1, or 2)¹¹, and we used a macro adapted from the NCI to calculate comorbidity weights¹². Patients who underwent autologous stem cell transplant, an independent risk factor for the development of zoster, were identified.

Use of zoster prophylaxis was defined as having 1 claim for oral acyclovir or valacyclovir during proteasome inhibitor treatment. Adherence was evaluated in users with 2 claims for antivirals, and was defined as a medication possession ratio (MPR) of 80% (days supplied by pharmacy divided by days between first and last prescriptions¹³). Multivariable logistic regression was used to evaluate variables associated with use and adherence.

Using proportional hazards modelling, we examined the development of zoster (ICD-9 053.x) in users and non-users of antivirals, and additionally in users who were adherent. When assessing for zoster, we only included patients who started an antiviral within 30 days of the index date and who developed infection after start of the antiviral, so as to approximate a cause-and-effect relationship between antiviral use and development of infection. To reduce bias from overfitting, we reduced the number of variables and included only those that appeared most clinically relevant to the development of zoster. For all models, the null hypothesis was rejected at the 0.05 level of significance. Data were analyzed using SAS 9.3 (SAS Institute, 2010) and RStudio (RStudio, 2016).

Of 70,687 patients identified with myeloma between 2009-2013, 6,934 (9.8%) received PIs for 3 months (Figure 1). Among them, 3,632 (52.4%) patients were dispensed zoster prophylaxis at least once (Table 1). Acyclovir was more commonly used than valacyclovir, accounting for 74% of total claims. Variables associated with increased use were younger age (adjusted odds ratio [AOR] 1.29; 95%CI 1.10-1.52 for 18-54 group), hospital-based practice settings (AOR 1.43; 95%CI 1.27-1.61 for outpatient hospital), active employment (AOR 1.19; 95%CI 1.01-1.41), more recent year (AOR 1.92; 95%CI 1.62-2.28 for 2013), increasing number of concurrent chemotherapy agents (AOR 2.92; 95%CI 1.98-4.41 for 3 agents), prior use of an antiherpetic agent (AOR 2.81; 95%CI 2.38-3.34), and lower comorbidity score (AOR 1.18; 95%CI 1.04-1.33 for 0). In our sensitivity analysis of the subset of patients who received proteasome inhibitors for 6 months, 1,391 out of 2,537 (54.8%) patients received zoster prophylaxis at least once. The results of the multivariate analysis are similar, although age and comorbidity score were no longer significant (additional data not shown).

Among the 3,632 patients receiving antivirals, 2,803 picked up an antiviral more than once. Of these, 2,356 (84%) were adherent (Table 2). Active employment (AOR 0.59; 95%CI 0.42-0.84) was associated with lower adherence, while calendar years except for 2010 (AOR

1.50; 95% CI 1.08-2.12 for 2013) and use of mail order pharmacies (AOR 2.22; 95% CI 1.19-4.60) were associated with greater adherence. For the 6-month cohort, younger age (AOR 0.51; 95% CI 0.32-0.79 for 18-54 age group compared with ≥ 65 years) was associated with lower adherence (additional data not shown).

Amongst users of antiviral prophylaxis, 60/2,450 (2.4%) developed zoster, and amongst non-users, 204/3,512 (5.8%) (Table 3). Receipt of antivirals (adjusted relative risk [ARR] 0.42; 95% CI 0.31-0.56), younger age (ARR 0.64; 95% CI 0.44-0.93 for 18-54 group), and use of acyclovir (ARR 0.53; 95% CI 0.29-0.99) were associated with lower risk. Unadjusted Kaplan-Meier curves for zoster infection are shown in Figure 2. In the cohort of patients who used proteasome inhibitors ≥ 6 months, both use of prophylaxis (24/915 or 2.6% in users versus 97/1,401 or 6.9% in nonusers; ARR 0.36, 95% CI 0.23-0.57) and adherence to prophylaxis (13/650 or 2.0% in adherent versus 9/193 or 4.7% in nonadherent; ARR 0.33, 95% CI 0.13-0.79) were independently associated with lower risk for zoster.

In summary, we found that 52% of myeloma patients treated with a proteasome inhibitor over a 3-month period received herpes zoster prophylaxis in accordance with guidelines. Amongst those who received an antiviral agent at least twice, adherence was 84% at 3 months. Use of antiviral agents was associated with fewer zoster infections – 2.4% vs 5.8% (ARR 0.42; 95% CI 0.31-0.56).

Though not life-threatening, zoster infections are associated with considerable morbidity and complications, including permanent scarring of the skin, postherpetic neuralgia, zoster ophthalmicus, myelitis or encephalitis, and cranial nerve palsies. Affected patients can experience significant or permanent compromises in quality of life. Retrospective analyses suggest that antivirals are effective in preventing zoster^{14,15}, but compliance to guidelines for prophylaxis has not been addressed in prior studies.

In our study, patients on multi-drug chemotherapy regimens were more likely to use antivirals compared to those on one or two drugs, possibly because they were considered to be more immunosuppressed. Patients who had been on anti-zoster therapy before starting proteasome inhibitors were also more likely to continue taking antivirals, presumably because they experienced a prior episode of shingles and wanted to prevent recurrence. Use of antivirals impacted the development of zoster infections, which is the biologically expected outcome. In both the 3 and 6-month cohorts, patients who received antiviral agents were significantly less likely to develop zoster. In examining stem cell transplant, we identified 32 cases of zoster among 628 patients (5.1%) who underwent transplant, versus 232 cases of zoster among 5,334 patients (4.3%) who did not undergo transplant. We did not have sufficient power to detect the effect of transplant upon zoster infection.

The overall incidence of zoster in our study is considerably lower than has been reported in clinical trials. For example, the VISTA study reported an incidence for zoster of 13% in patients who received bortezomib-containing treatment but no prophylaxis, and 3% in those receiving bortezomib-containing treatment with prophylaxis⁶. We suspect this difference is due to the more rigorous monitoring of patients and recording of adverse events provided by

clinical trials, and under-reporting of zoster diagnoses in claims-based databases – physicians may not enter a code for zoster if it is not the main reason for a visit.

Our study has important limitations. We do not know how many clinicians prescribed antiviral agents, how many patients received prescriptions, and reasons for why patients did not pick up their prescriptions or were nonadherent. We assume that patients who picked up prescriptions took the medications, but this cannot be verified. There are many aspects of adherence that the MPR measure does not capture, such as whether patients took the correct doses at consistent times, and whether there were missed doses or extra doses. We did not have disease-based covariates, such as stage, line of chemotherapy, or results of bone marrow or serum studies. There is likely under-capture of zoster infections given that they do not tend to be life-threatening events, and our model for the development of zoster does not consider the competing risk of death as this information is not available in our database. Our database does not provide information about race, and is only generalizable to the insured population of the U.S.

Though use of antiviral prophylaxis in myeloma patients on proteasome inhibitors improved from 46% of patients in 2009 to 62% in 2013, many in our study still did not receive this effective and guideline-recommended prevention measure. Given the importance of proteasome inhibitors and their prevalent use in the treatment of myeloma, we hope to raise awareness of the need for zoster prophylaxis in this patient population.

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Figure 1. Selection of study population

The following steps were used to identify adult myeloma patients on proteasome inhibitor chemotherapy and who have outpatient drug claims in the Truven MarketScan database.

Figure 2. Kaplan-Meier plot of probability of remaining free from zoster infection

In the 3-month cohort, users of antiviral prophylaxis had a significantly higher probability of remaining zoster free compared to nonusers ($P < .0001$). A similar result was noted in the 6-month cohort. Note the vertical axis has been truncated to facilitate visual comparison.

Table 1
Use of herpes zoster prophylaxis

Descriptive statistics and multivariate regression analyses for receipt of zoster prophylaxis in myeloma patients on proteasome inhibitor therapy for at least 3 months between 2009-2013 in the Truven MarketScan database (n = 6,934). Results that are statistically significant are in bold. NA = not applicable; REF = reference group.

Characteristic	No. (%)	Dispensed (%)	Adjusted OR (95%CI) for Dispensed
Total	6,934	3,632 (52.4%)	NA
Age group at index			
18-54	1,473 (21.2)	867 (58.9)	1.29 (1.10, 1.52)
55-64	2,711 (39.1)	1,488 (54.9)	1.16 (1.02, 1.32)
65	2,750 (39.7)	1,277 (46.4)	REF
Sex			
Male	3,906 (56.3)	2,067 (52.9)	1.05 (0.95, 1.16)
Female	3,028 (43.7)	1,565 (51.7)	REF
Region			
Northeast	1,392 (20.1)	828 (59.5)	1.70 (1.47, 1.96)
North Central	1,959 (28.3)	1,054 (53.8)	1.45 (1.27, 1.65)
West	1,153 (16.6)	618 (53.6)	1.34 (1.16, 1.56)
South	2,353 (33.9)	1,095 (46.5)	REF
MSA ^a			
Yes	5,889 (84.9)	3,112 (52.8)	REF
No	970 (14.0)	485 (50.0)	0.94 (0.82, 1.10)
Place of service			
Office	2,934 (42.3)	1,366 (46.6)	REF
Outpatient hospital	2,125 (30.6)	1,247 (58.7)	1.43 (1.27, 1.61)
Inpatient	1,203 (17.3)	649 (53.9)	1.24 (1.07, 1.44)
Other ^b	672 (9.7)	370 (55.1)	1.29 (1.08, 1.54)
Employment status			
Actively employed	1,562 (22.5)	911 (58.3)	1.19 (1.01, 1.41)
Other/unknown	2,855 (41.2)	1,554 (54.4)	1.18 (1.03, 1.35)
Retired	2,517 (36.3)	1,167 (46.4)	REF
Benefit plan			
Comprehensive	1,127 (16.3)	514 (45.6)	REF
PPO	3,895 (56.2)	2,071 (53.2)	1.09 (0.93, 1.27)
HMO	822 (11.9)	433 (52.7)	1.00 (0.81, 1.23)
POS	388 (5.6)	208 (53.6)	1.10 (0.85, 1.42)
Other ^c	702 (10.1)	406 (57.8)	1.09 (0.88, 1.37)
Year			

Characteristic	No. (%)	Dispensed (%)	Adjusted OR (95%CI) for Dispensed
2009	2,256 (32.5)	1,045 (46.3)	REF
2010	1,277 (18.4)	631 (49.4)	1.17 (1.01, 1.35)
2011	1,373 (19.8)	721 (52.5)	1.28 (1.11, 1.47)
2012	1,201 (17.3)	722 (60.1)	1.75 (1.51, 2.04)
2013	827 (11.9)	513 (62.0)	1.92 (1.62, 2.28)
# chemotherapy ^d			
1	3,755 (54.2)	1,719 (45.8)	REF
2	3,043 (43.9)	1,813 (59.6)	1.56 (1.41, 1.73)
3	136 (2.0)	100 (73.5)	2.92 (1.98, 4.41)
Prior diagnosis herpes			
Yes	101 (1.5)	66 (65.3)	1.51 (0.98, 2.36)
No	6,833 (98.5)	3,566 (52.2)	REF
Prior antiviral agent			
Yes	816 (11.8)	599 (73.4)	2.81 (2.38, 3.34)
No	6,118 (88.2)	3,033 (49.6)	REF
Baseline Charlson			
0	4,169 (60.1)	2,259 (54.2)	1.18 (1.04, 1.33)
1	1,012 (14.6)	511 (50.5)	1.02 (0.87, 1.20)
2	1,753 (25.3)	862 (49.2)	REF
Stem cell transplant			
Yes	702 (10.1)	313 (44.6)	0.88 (0.74, 1.04)
No	6,232 (89.9)	3,319 (53.3)	REF

^aMetropolitan statistical area

^bOther places of service denote: independent laboratory, and emergency room

^cOther benefit plans denote: EPO (Exclusive Provider Organization), CDHP (Consumer-Driven Health Plan), HDHP (High-Deductible Health Plan)

^dNumber of concurrent chemotherapy agents given; 1 indicates proteasome inhibitor only. Does not include steroids

Table 2
Adherence to herpes zoster prophylaxis

Descriptive statistics and multivariate analyses for adherence to zoster prophylaxis in myeloma patients receiving proteasome inhibitor therapy for at least 3 months between 2009-2013 in the Truven MarketScan database (n = 2,803). Adherence is defined as having a medication possession ratio (MPR; the sum of all days supplied by the pharmacy divided by the number of days between the first and last prescription) ≥ 80%. Results that are statistically significant are in bold. NA = not applicable; REF = reference group.

Characteristic	No. (%)	Adherent (%)	Adjusted OR (95% CI) for Adherence
Total	2,803	2,356 (84.1%)	NA
Age group at index			
18-54	684 (24.4)	557 (81.4)	1.08 (0.78, 1.51)
55-64	1150 (41.0)	975 (84.8)	1.27 (0.95, 1.70)
65	969 (34.6)	824 (85.0)	REF
Sex			
Male	1,604 (57.2)	1,365 (85.1)	1.21 (0.99, 1.49)
Female	1,199 (42.8)	991 (82.7)	REF
Region			
Northeast	669 (23.9)	556 (83.1)	1.12 (0.85, 1.49)
North central	831 (29.6)	712 (85.7)	1.30 (0.99, 1.72)
West	465 (16.6)	405 (87.1)	1.60 (1.15, 2.25)
South	806 (28.8)	654 (81.1)	REF
MSA ^a			
Yes	2,402 (85.7)	2,009 (83.6)	REF
No	371 (13.2)	320 (86.3)	1.22 (0.89, 1.70)
Place of service			
Office	1,004 (35.8)	834 (83.1)	REF
Outpatient hospital	992 (35.4)	846 (85.3)	1.21 (0.94, 1.55)
Inpatient	518 (18.5)	444 (85.7)	1.24 (0.91, 1.70)
Other ^b	289 (10.3)	232 (80.3)	0.82 (0.58, 1.16)
Employment status			
Actively employed	719 (25.7)	583 (81.1)	0.59 (0.42, 0.84)
Other/unknown	1,215 (43.3)	1,018 (83.8)	0.76 (0.56, 1.03)
Retired	869 (31.0)	755 (86.9)	REF
Benefit plan			
Comprehensive	386 (13.8)	336 (87.0)	REF
PPO	1,594 (56.9)	1,345 (84.4)	0.93 (0.63, 1.34)
HMO	342 (12.2)	282 (82.5)	0.85 (0.54, 1.35)
POS	164 (5.9)	136 (82.9)	0.88 (0.51, 1.53)
Other ^c	317 (11.3)	257 (81.1)	0.75 (0.45, 1.23)

Characteristic	No. (%)	Adherent (%)	Adjusted OR (95% CI) for Adherence
Year			
2009	750 (26.8)	602 (80.3)	REF
2010	504 (18.0)	420 (83.3)	1.27 (0.94, 1.72)
2011	564 (20.1)	491 (87.1)	1.73 (1.27, 2.38)
2012	564 (20.1)	485 (86.0)	1.59 (1.17, 2.18)
2013	421 (15.0)	358 (85.0)	1.50 (1.08, 2.12)
Pharmacy type			
Retail	2,540 (90.6)	2,130 (83.9)	REF
Mail order	113 (4.0)	103 (91.2)	2.22 (1.19, 4.60)
Unknown	150 (5.4)	123 (82.0)	1.05 (0.65, 1.76)
# chemotherapy ^d			
1	1,274 (45.5)	1,070 (84.0)	REF
2	1,445 (51.6)	1,216 (84.2)	0.99 (0.80, 1.24)
3	84 (3.0)	70 (83.3)	1.00 (0.56, 1.90)
Prior diagnosis of herpes			
Yes	43 (1.5)	38 (88.4)	1.57 (0.66, 4.64)
No	2,760 (98.5)	2,318 (84.0)	REF
Prior antiviral agent			
Yes	449 (16.0)	366 (81.5)	0.83 (0.63, 1.10)
No	2,354 (84.0)	1,990 (84.5)	REF
Post-index antiviral agent			
Acyclovir	2,108 (75.2)	1,775 (84.2)	REF
Valacyclovir	695 (24.8)	581 (83.6)	1.01 (0.80, 1.29)
Baseline Charlson			
0	1,766 (63.0)	1,491 (84.4)	1.25 (0.97, 1.61)
1	389 (13.9)	327 (84.1)	1.12 (0.79, 1.60)
2	648 (23.1)	538 (83.0)	REF
Stem cell transplant			
Yes	218 (7.8)	184 (8.4)	1.01 (0.69, 1.52)
No	2,585 (92.2)	2,172 (84.0)	REF

^aMetropolitan statistical area

^bOther places of service denote: independent laboratory, emergency room

^cOther benefit plans denote: EPO (Exclusive Provider Organization), CDHP (Consumer-Driven Health Plan), HDHP (High-Deductible Health Plan)

^dNumber of concurrent chemotherapy agents given; 1 indicates proteasome inhibitor only. Does not include steroids

Table 3
Herpes zoster infections by use of antiviral agents, and adherence to antiviral agents

Adjusted relative risk by proportional hazards regression for the development of zoster infections in myeloma patients who received at least 3 months of proteasome inhibitor therapy between 2009-2013 in the Truven MarketScan database. Results that are statistically significant are in bold. NA = not applicable; REF = reference group.

Characteristic	Use	Adherence
Status		
Yes	0.42 (0.31, 0.56)	0.76 (0.37, 1.55)
No	REF	REF
Age group at index		
18-54	0.64 (0.44, 0.93)	0.40 (0.15, 1.10)
55-64	0.92 (0.71, 1.21)	1.30 (0.69, 2.44)
65	REF	REF
Sex		
Male	1.01 (0.79, 1.29)	0.56 (0.31, 1.01)
Female	REF	REF
# of chemotherapy agents		
1	REF	REF
2	1.00 (0.78, 1.29)	0.86 (0.47, 1.56)
Prior antiviral agent		
Yes	1.43 (1.00, 2.04)	1.19 (0.59, 2.43)
No	REF	REF
Baseline Charlson		
0	REF	REF
1	0.79 (0.54, 1.15)	0.94 (0.39, 2.27)
2	0.97 (0.73, 1.30)	0.92 (0.45, 1.92)
Post index antiviral agent		
Acyclovir	NA	0.53 (0.29, 0.99)
Valacyclovir		REF
Stem cell transplant		
Yes	0.72 (0.41, 1.24)	0.60 (0.21, 1.69)
No	REF	REF