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Quality and Outcomes of Treatment of Hypercalcemia of Malignancy

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Abstract

Using a nationwide database, 4874 patients with hypercalcemia of malignancy were identified. The in-hospital mortality rate was 6.8%. Overall, 1971 (40.4%) patients received pamidronate and 1399 (28.7%) received zoledronic acid during hospitalization. Calcitonin was utilized in 1337 (27.4%) patients while glucocorticoids were administered to 1311 (26.9%). Use of contraindicated medications was noted in 136 (2.8%) patients who received thiazide diuretics and 12 (0.2%) who received lithium. Tumor site, presence of bone metastases, and severity of illness were predictors of treatment. There was no association between treatment with bisphosphonates, calcitonin, or glucocorticoids and morbidity or mortality.

Introduction

Among cancer patients, up to one third will experience hypercalcemia at some point during their disease course.^{1–4} Secretion of parathyroid hormone-related protein (PTHrP) is the most common cause of hypercalcemia of malignancy and is associated with up to 80% of cases.¹ Bone metastases and increased osteoclastic activity account for the majority of the remaining cases of hypercalcemia of malignancy.^{1–3} Although the symptoms of hypercalcemia of malignancy are often mild and non-specific, the resulting metabolic derangements can be rapid and associated with substantial morbidity and mortality. It is estimated that 50% of cancer patients with hypercalcemia die within 30 days.^{1,5}

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Treatment of hypercalcemia of malignancy relies on hydration, calciuresis, and inhibition of osteoclast-induced bone resorption. Drugs that increase serum calcium levels such as thiazide diuretics and lithium should be discontinued. Intravenous bisphosphonates are now the preferred agents for the initial management of hypercalcemia of malignancy.^{1,3,6,7} While both pamidronate and zoledronic acid are effective, zoledronic acid has been associated with a slight improvement in the reduction of calcium levels.⁶

Second-line agents used for the management of hypercalcemia of malignancy include calcitonin and glucocorticoids, both of which are occasionally used, while other drugs, such as mithramycin and gallium nitrate, have largely been replaced by the bisphosphonates.¹⁻³ The receptor activator of nuclear factor κ B ligand (RANKL) antibody denosumab was recently approved for the prevention of skeletal related events in patients with bone metastases and may have a role in the management of hypercalcemia of malignancy.^{1,3,8}

Despite the morbidity associated with hypercalcemia of malignancy, consensus recommendations for treatment are largely lacking and little is known about the quality of care cancer patients with hypercalcemia receive. We examined the quality of care and outcomes of patients admitted with a primary diagnosis of hypercalcemia of malignancy. Specifically, we analyzed adherence to evidence-based treatment for cancer patients with hypercalcemia and explored the associations between initial patterns of care and outcomes.

Methods

Data Source

Data from the Perspective database (Premier, Charlotte, North Carolina) was used for analysis. Perspective captures hospital encounters from more than 500 hospitals across the United States. The database includes detailed demographic data, diagnoses, procedures and all services rendered to patients during hospitalization. The data from Perspectives undergoes a multistep quality control process and the dataset has been utilized for a number of outcomes studies.⁹⁻¹² In 2006, the database contained approximately 5.5 million discharges, representing approximately 15% of all hospitalizations in the U.S.⁹

Patient Selection

Cancer patients with hypercalcemia from 2006–2012 were analyzed. Only patients with an admitting or primary diagnosis of hypercalcemia (ICD9 code 275.42) in combination with an ICD9 code for a malignancy were included. The analysis was limited to only those patients with an admitting or primary diagnosis of hypercalcemia to capture initial decision-making and treatment as previously described.¹³ Only the first hospital admission was examined for patients with multiple episodes of care for hypercalcemia. Tumors were categorized into the following sites: breast, lung, multiple myeloma, gastrointestinal, gynecologic, genitourinary and other primary sites (including brain, soft tissue, skin, and head and neck). To further capture the severity of underlying illness, we analyzed the presence of a number of concurrent medical conditions, including bone metastases, acute and chronic renal failure, respiratory failure, bacteremia and shock, and hypotension, as well

as medical services including mechanical ventilation and intensive care unit admission using diagnosis and charge codes as previously described.^{10,13,14}

Clinical, Demographic, and Disease-Specific Characteristics

Clinical characteristics, including age (<50, 50–59, 60–69, and 70 years), gender, date of admission, race (white, black, and other), marital status (married, single or unknown), and insurance status (commercial, Medicare, Medicaid, uninsured, and unknown) were recorded for each patient. Risk adjustment for comorbid conditions was performed using the Charlson comorbidity index.^{15,16}

The specialty of each patient's primary admitting physician was classified as medical oncology (including hematology), internal medicine (including subspecialties other than medical oncology), hospitalist, family practice, and other specialty. Hospitals in which patients were treated were characterized based on location (metropolitan, non-metropolitan), region of the country (northeast, midwest, west, south), size (<400 beds, 400–600 beds, and >600 beds) and teaching status (teaching, non-teaching). Each hospital's annual volume of patients with hypercalcemia was estimated by dividing the number of subjects admitted with hypercalcemia by the number of years a given hospital contributed at least one hypercalcemia patient to the cohort. The volume estimates were then visually inspected and cut-points chosen to create three approximately equal tertiles: low (<2.4 cases/year), intermediate (2.41–3.5 cases/year) and high (>3.5 cases/year) as previously described.^{13,17,18}

Outcomes

The primary outcomes of the study were use of evidence-based treatments for hypercalcemia and avoidance of therapies that worsen hypercalcemia. These outcomes were based on a review of the published literature describing best-practice treatments.^{1–3,6,7} Prompt administration of either zoledronic acid or pamidronate is recommended for most patients with hypercalcemia of malignancy.^{1–3} We examined use of either of these agents within 48 hours of admission. Use of other ancillary treatments including calcitonin, denosumab, mithramycin, gallium nitrate, and glucocorticoids, was also explored.^{1–3} We examined use of contraindicated medications for patients with hypercalcemia including other bisphosphonates (bisphosphonates other than zoledronic acid or pamidronate) and medications that increase serum calcium levels (thiazide diuretics and lithium).¹ Lastly, we explored the use of diagnostic testing with bone scans. Descriptive data for the timing of use of each outcome is reported (within 48, 72 or 96 hours of admission or at any point during the hospitalization).

We examined the association between clinical and demographic characteristics as well as treatment on adverse outcomes. Adverse outcomes of interest included non-routine discharge (discharge to a nursing home, skilled nursing facility, or acute or sub-acute rehabilitation center), in-hospital mortality, and prolonged hospitalization. Prolonged hospitalization was defined as hospitalization for longer than the 75th percentile (>8 days).

Statistical Analysis

Frequency distributions between categorical variables were compared using χ^2 tests. To examine the associations between treatments of interest and outcomes, we fit log-linear (Poisson) regression models based on the method of generalized estimating equations. These models included all patient, physician, and hospital characteristics and accounted for hospital-level clustering. Associations are reported as risk ratios (RR) and 95% confidence intervals (CI).

To examine the associations between the treatments of interest and outcomes, we developed a matched propensity score analysis to limit the influence of confounding on treatment selection. The propensity score was estimated as the probability that a patient received the treatment of interest within a given time period.^{19–21} Initially, a propensity score was estimated for receipt of the bisphosphonates pamidronate or zoledronic acid within 48 hours of admission. Separate propensity scores were also derived for use of calcitonin and glucocorticoids, both within 48 hours of admission. Each patient's propensity score was estimated from a multivariable logistic regression model that included the demographic, clinical, hospital, and physician variables described above as well as other treatments of hypercalcemia.

For each propensity score, a series of models were developed and the goodness of fit of each model assessed. The final model included all of the demographic, clinical, hospital, and physician characteristics as well as two-way interaction terms with a P-value of <0.15. The final model best fit the data as evidenced by the smallest Akaike information criterion and a c-statistic of 0.73. After the calculation of each patient's propensity score, we performed a 5 to 1 greedy match between the patients who received a given treatment and those who did not. We evaluated the matches between the groups by calculating the standardized difference, with a standardized difference score ≤ 0.1 for covariates considered to indicate a good match.²² To further analyze the goodness of fit of the matching, the propensity scores of treated and untreated subjects were plotted and visually inspected before and after matching.

Morbidity, mortality, and resource utilization were compared between the propensity-matched groups using conditional logistic regression procedures, with the matched odds ratios and 95% confidence intervals as the effect measure. A series of sensitivity analyses were performed in which propensity score matching was based on a preset caliper (0.10) or using a nearest neighbor matching approach. Additionally, the outcomes of interest were compared after propensity score stratification into five groups as well as propensity score stratification into deciles. Statistical analyses were performed with SAS version 9.4 (SAS Institute Inc, Cary, North Carolina). A P-value of <0.05 was considered statistically significant.

Results

A total of 4874 patients treated at 482 hospitals with a primary diagnosis of hypercalcemia of malignancy were identified. Within the cohort, 28.5% of the patients were 60–69 years of age and 42.9% were ≥ 70 years old (Table 1). The most common tumor sites were lung

cancer (27.2%), multiple myeloma (23.6%) and breast cancer (15.0%). Bone metastases were identified in 1292 (26.5%) patients. The median length of stay was 4 days (interquartile range, 2–8 days) and the in-hospital mortality rate was 6.8%.

Table 2 displays the treatments rendered during hospitalization. Overall, 1971 (40.4%) patients received pamidronate and 1399 (28.7%), zoledronic acid at some point during hospitalization. Within 48 hours of admission, pamidronate was administered to 1565 (32.1%) patients and zoledronic acid to 1093 (22.4%). Either zoledronic acid or pamidronate or both were administered to 2642 (54.2%) within 48 hours and to 3303 (67.8%) during admission. Calcitonin was utilized in 1337 (27.4%) patients, including 1088 (22.3%) who received calcitonin within 48 hours of admission, while glucocorticoids were administered to 1311 (26.9%) patients at some point and to 744 (15.3%) within 48 hours of hospitalization. Other bisphosphonates and other second-line agents were rarely utilized. Use of contraindicated medications that raise serum calcium levels was noted in 136 (2.8%) patients who received thiazide diuretics and 12 (0.2%) who received lithium. Pamidronate or zoledronic acid were administered to 950 (72.2%) of 1315 patients with acute renal failure and to 594 (68.8%) of 863 with chronic renal insufficiency.

In a multivariable model, patients with bone metastases were 28% more likely to receive either pamidronate or zoledronic acid (RR=1.28; 95% CI, 1.21–1.36) (Table 3). Compared to breast cancer patients, those with other tumors were more likely to receive one of these agents. Patients with greater comorbidity were more likely to receive pamidronate or zoledronic acid, while residents in rural areas were 11% less likely to receive one of the drugs (RR=0.89; 95% CI, 0.80–0.99). Patients with acute renal failure were 7% (RR=0.93; 95% CI, 0.87–0.99) less likely to receive a bisphosphonate, while patients treated with either calcitonin or glucocorticoids were more likely to receive bisphosphonate.

Use of calcitonin within 48 hours of admission increased in more recent years, was more frequent in subjects with bone metastases (RR=1.25; 95% CI, 1.09–1.42), in black patients (RR=1.18; 95% CI, 1.03–1.34), in patients treated by non-oncology specialists, in those with acute renal failure (RR=1.73; 95% CI, 1.52–1.95), in patients with multiple myeloma (RR=1.26; 95% CI, 1.02–1.56) and in subjects who also received glucocorticoids or bisphosphonates. Age, tumor type, comorbidity, specialty of the attending physician and other medical conditions were predictive of receipt of glucocorticoids. Factors associated with receipt of contraindicated medications (thiazide diuretics and lithium) included residence in the southern U.S. (RR=1.78; 95% CI, 1.10–2.89) and bone metastases (RR=1.55; 95% CI, 1.06–2.27).

The characteristics of patients who received zoledronic acid or pamidronate within 48 hours of admission after propensity score matching are displayed in Table 1. The standardized differences between the groups within the matched cohort demonstrated good matching. After matching, there was no association between prompt initiation of zoledronic acid or pamidronate and outcomes (Table 4). For example, the odds ratio for prolonged hospitalization with receipt of bisphosphonate was 0.88 (95% CI, 0.72–1.02), 1.09 (95% CI, 0.93–1.27) for non-routine discharge, and 1.05 (95% CI, 0.80–1.39) for death.

Similar findings were noted for administration of calcitonin and glucocorticoids within 48 hours of admission (matched characteristics Supplementary Tables 1 and 2). Neither calcitonin nor glucocorticoids were associated with length of hospitalization, non-routine discharge, or in-hospital mortality (Table 4). A series of sensitivity analyses were performed matching patients by alternate calipers or a nearest neighbor approaching or through stratification. The results of all of these analyses were largely unchanged; there was no association with initial treatment and outcomes.

Discussion

We noted that outcomes for hypercalcemia of malignancy was poor and there was widespread variation in the quality of care for these patients. First-line therapeutic agents were frequently omitted, while agents of uncertain therapeutic benefit and contraindicated drugs were given relatively commonly. Regardless of initial treatment and decision-making, we were unable to demonstrate an association between treatment and outcomes.

Although the bisphosphonates zoledronic acid and pamidronate are widely considered the standard of care for hypercalcemia of malignancy, we noted that 33% of patients failed to receive one of these agents as part of their treatment.^{1–3} For those patients who received bisphosphonate therapy, it was generally administered in a timely manner; 79% received the drugs within 48 hours of admission. Treatment recommendations call for administration of bisphosphonates as soon as hypercalcemia is diagnosed as reduction in serum calcium levels typically are not seen for 2–4 days.¹ Reassuringly, older generation bisphosphonates with less therapeutic efficacy were used very infrequently.

We noted that drugs of uncertain benefit were utilized relatively frequently in patients with hypercalcemia. In our cohort, both calcitonin and glucocorticoids were each administered to over a quarter of patients. Calcitonin provides a rapid reduction in serum calcium levels (12 to 24 hours), but the reductions are often small and transient.^{1,3} In contrast, glucocorticoids lower serum calcium levels over 3–5 days and may have efficacy in some patients, especially those with lymphomas.^{1,3} Both of these agents were used frequently and the use of calcitonin appears to be rising year after year. Our findings are notable in that these drugs were not only commonly used as adjuncts to bisphosphonates, but also frequently utilized without bisphosphonates even in patients without a clear contraindication to bisphosphonate therapy.

Use of contraindicated drugs was also relatively common. We found that 3% of patients used drugs that increase serum calcium levels, such as lithium and thiazide diuretics. Further, renal insufficiency, a relative contraindication to the use of bisphosphonates, had only a modest impact on prescribing patterns among clinicians. In clinical trials, patients with renal dysfunction were excluded and bisphosphonate use may worsen kidney function in those with underlying renal insufficiency; however, in our cohort, 71% of patients with acute or chronic renal failure received a bisphosphonate.^{23–26} This is in accord with other work that has demonstrated that many drugs are used in scenarios in which they are contraindicated.^{27–30} A study of cancer patients receiving bevacizumab noted that 36% of patients had a contraindication to use, while 22% of patients undergoing dialysis and a

percutaneous coronary intervention received contraindicated antithrombotic medication.^{27,28} While in some scenarios the benefits of use of a drug may outweigh the potential risks, many instances of contraindicated drug use likely stem from lack of awareness of the contraindication.

Among patients with hypercalcemia of malignancy, we found no association between use of bisphosphonates and reduced morbidity or mortality. Prior studies examining compliance with evidenced-based recommendations from clinical trials and population-level outcomes have often shown weak, if any, correlation between adherence to best practice process measures and outcomes.^{31–35} A large study that analyzed compliance with perioperative antibiotic prophylaxis, a national quality metric, and wound infections, found no association between any of the individual, publically reported measures of antibiotic use and infection rates.³⁵ Similarly, high performance on process measures for myocardial infarction, pneumonia and heart failure has only a small impact on mortality.³¹ It is increasingly recognized that adherence to best practice process measures is often a surrogate for a complex array of underlying hospital characteristics and unmeasured factors.³⁴ Further, for hypercalcemia of malignancy, randomized trials comparing various therapeutic interventions are limited and many recommendations are based on expert opinion. These findings indicate that regardless of therapeutic choice, lowering serum calcium may be the most important goal of therapy. Further, hypercalcemia of malignancy is associated with a poor prognosis and likely an end of life event for many cancer patients.

A number of factors were associated with the allocation of care and outcomes. Patients with multiple myeloma were more likely to receive not only bisphosphonates, but also calcitonin and glucocorticoids, likely reflecting more significant underlying hypercalcemia. Similarly, patients with bone metastases and other conditions signifying acute illness more often were treated with not only bisphosphonates, but also calcitonin and glucocorticoids. Lastly, the specialty of the treating physician was associated with care. Compared to patients managed by oncologists, those primarily cared for by hospitalists or family practice physicians were more likely to receive calcitonin and less likely to receive glucocorticoids. Prior studies have shown that care by hospitalists may improve guideline adherence and reduce costs in some clinical scenarios.^{13,36}

While our study benefits from the inclusion of a large number of patients, we recognize a number of important limitations. Perhaps most importantly, we lack data on the actual serum calcium levels for patients within the cohort. To mitigate this limitation, we included only patients with a primary or admitting diagnosis of hypercalcemia and analyzed treatments that are generally recommended regardless of the actual calcium levels. We lack data on longitudinal follow-up, and, as such, analyzed only in-hospital mortality. A priori the goal of our analysis was to examine how initial treatment and decision-making were associated with short-term outcomes. As with any observational study based on administrative data, we were unable to perform complete risk adjustment for the cohort. To limit this bias, we included a large number of inpatient medical conditions into our risk adjustment models and we performed a number of sensitivity analyses in which our findings were largely unchanged. Lastly, we lack data on individual patient and physician preferences that undoubtedly influenced treatment planning.

Despite the morbidity and mortality associated with hypercalcemia of malignancy, the overall quality of care for this condition is highly variable. While recommended therapies are often omitted, the utilization of treatments of uncertain benefit as well as therapeutic interventions that may be harmful are also common. In addition to institutional interventions to improve the quality of care for cancer patients with hypercalcemia, national efforts to recognize the treatment of hypercalcemia as a quality metric may be warranted.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Clinical and demographic characteristics of the cohort. Left column displays the characteristics of the entire cohort, right columns display characteristics of the propensity score matched cohort for receipt of bisphosphonates within 48 hours of admission.

	Entire Cohort		Propensity Score Matched Cohort		No bisphosphonate		Bisphosphonate		SD
	N	(%)	N	(%)	N	(%)	N	(%)	
<i>Age</i>	4874		1635	(50.0)	1635	(50.0)			0.018
<50	415	(8.5)	136	(8.3)	143	(8.8)			
50–59	976	(20.0)	319	(19.5)	323	(19.8)			
60–69	1391	(28.5)	455	(27.8)	449	(27.5)			
70	2092	(42.9)	725	(44.3)	720	(44.0)			
<i>Gender</i>									0.023
Male	2448	(50.2)	812	(49.7)	793	(48.5)			
Female	2426	(49.8)	823	(50.3)	842	(51.5)			
<i>Year of diagnosis</i>									0.040
2006	504	(10.3)	174	(10.6)	171	(10.5)			
2007	547	(11.2)	171	(10.5)	186	(11.4)			
2008	569	(11.7)	201	(12.3)	196	(12.0)			
2009	635	(13.0)	213	(13.0)	204	(12.5)			
2010	747	(15.3)	242	(14.8)	241	(14.7)			
2011	888	(18.2)	297	(18.2)	309	(18.9)			
2012	984	(20.2)	337	(20.6)	328	(20.1)			
<i>Race</i>									0.017
White	3184	(65.3)	1060	(64.8)	1073	(65.6)			
Black	902	(18.5)	310	(19.0)	304	(18.6)			
Other	788	(16.2)	265	(16.2)	258	(15.8)			
<i>Marital status</i>									0.028
Married	2287	(46.9)	744	(45.5)	763	(46.7)			
Single	2073	(42.5)	727	(44.5)	704	(43.1)			

	Entire Cohort		Propensity Score Matched Cohort			
			No bisphosphonate		Bisphosphonate	
	N	(%)	N	(%)	N	(%)
Unknown	514	(10.5)	164	(10.0)	168	(10.3)
Insurance status						
Commercial	1319	(27.1)	437	(26.7)	443	(27.1)
Medicare	2831	(58.1)	969	(59.3)	960	(58.7)
Medicaid	449	(9.2)	146	(8.9)	146	(8.9)
Uninsured	179	(3.7)	56	(3.4)	59	(3.6)
Unknown	96	(2.0)	27	(1.7)	27	(1.7)
Comorbidity						
1	76	(1.6)	15	(0.9)	21	(1.3)
2	109	(2.2)	32	(2.0)	31	(1.9)
3	4689	(96.2)	1588	(97.1)	1583	(96.8)
Primary tumor site						
Breast	732	(15.0)	235	(14.4)	229	(14.0)
Lung	1325	(27.2)	432	(26.4)	425	(26.0)
Myeloma	1148	(23.6)	427	(26.1)	429	(26.2)
Gastrointestinal	489	(10.0)	158	(9.7)	163	(10.0)
Gynecologic	214	(4.4)	69	(4.2)	77	(4.7)
Genitourinary	677	(13.9)	226	(13.8)	222	(13.6)
Other	289	(5.9)	88	(5.4)	90	(5.5)
Area of residence						
Urban	4117	(84.5)	1382	(84.5)	1382	(84.5)
Rural	757	(15.5)	253	(15.5)	253	(15.5)
Hospital teaching status						
Non-teaching	2973	(61.0)	1002	(61.3)	991	(60.6)
Teaching	1901	(39.0)	633	(38.7)	644	(39.4)
Region						
Northeast	1053	(21.6)	364	(22.3)	372	(22.8)
Midwest	840	(17.2)	258	(15.8)	265	(16.2)

	Entire Cohort		Propensity Score Matched Cohort				
			No bisphosphonate				
	N	(%)	N	(%)	N	(%)	SD
South	2141	(43.9)	728	(44.5)	738	(45.1)	
West	840	(17.2)	285	(17.4)	260	(15.9)	
Hospital bed size							0.012
<400	2654	(54.5)	897	(54.9)	900	(55.1)	
400–600	1296	(26.6)	430	(26.3)	422	(25.8)	
>600	924	(19.0)	308	(18.8)	313	(19.1)	
Hospital volume							0.012
Low	1641	(33.7)	559	(34.2)	567	(34.7)	
Intermediate	1591	(32.6)	532	(32.5)	532	(32.5)	
High	1642	(33.7)	544	(33.3)	536	(32.8)	
Attending physician specialty							0.030
Hematology/oncology	1479	(30.3)	498	(30.5)	516	(31.6)	
Family practice	433	(8.9)	143	(8.8)	149	(9.1)	
Hospitalist	761	(15.6)	223	(13.6)	217	(13.3)	
Other	2201	(45.2)	771	(47.2)	753	(46.1)	
Bone metastasis	1292	(26.5)	411	(25.1)	407	(24.9)	−0.006
Acute renal failure	1315	(27.0)	453	(27.7)	451	(27.6)	−0.003
Chronic renal failure	863	(17.7)	301	(18.4)	313	(19.1)	0.019
Hypotension	165	(3.4)	54	(3.3)	46	(2.8)	−0.028
Bacteremia	155	(3.2)	40	(2.5)	39	(2.4)	−0.004
Shock	164	(3.4)	53	(3.2)	44	(2.7)	−0.032
Respiratory failure	264	(5.4)	78	(4.8)	75	(4.6)	−0.009
ICU admission	523	(10.7)	156	(9.5)	159	(9.7)	0.006
Mechanical ventilation	86	(1.8)	28	(1.7)	26	(1.6)	−0.010
Use of other medications							
Calcitonin	-	-	337	(20.6)	336	(20.6)	−0.002
Glucocorticoids	-	-	247	(15.1)	253	(15.5)	0.010
Contraindicated medications	-	-	36	(2.2)	36	(2.2)	0

SD refers to the standardized difference in the proportions between patients that did and did not receive bisphosphonate treatment.

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Table 2

Treatments utilized for patients with hypercalcemia of malignancy.

	Within 48-hours		Within 72-hours		Within 96-hours		Anytime during hospitalization	
	N	(%)	N	(%)	N	(%)	N	(%)
<i>Recommended bisphosphonates</i>								
Zoledronic acid	1093	(22.4)	1197	(24.6)	1253	(25.7)	1399	(28.7)
Pamidronate	1565	(32.1)	1693	(34.7)	1775	(36.4)	1971	(40.4)
<i>Second-line agents</i>								
Calcitonin	1088	(22.3)	1197	(24.6)	1248	(25.6)	1337	(27.4)
Denosumab	4	(0.08)	6	(0.1)	8	(0.2)	10	(0.2)
Mithramycin	0	-	0	-	0	-	0	-
Gallium nitrate	2	(0.04)	2	(0.04)	3	(0.06)	5	(0.1)
Plicamycin	1	(0.02)	1	(0.02)	1	(0.02)	1	(0.02)
Glucocorticoids	744	(15.3)	889	(18.2)	983	(20.2)	1311	(26.9)
<i>Other bisphosphonates</i>								
Risedronate	3	(0.06)	4	(0.08)	4	(0.08)	6	(0.1)
Ibandronate	1	(0.02)	1	(0.02)	1	(0.02)	1	(0.02)
Alendronate	15	(0.3)	19	(0.4)	22	(0.5)	28	(0.6)
Etidronate	2	(0.04)	2	(0.04)	3	(0.06)	4	(0.08)
Clodronate	0	-	0	-	0	-	0	-
<i>Contraindicated medications</i>								
Thiazide diuretics	100	(2.1)	105	(2.2)	110	(2.3)	136	(2.8)
Lithium	11	(0.2)	11	(0.2)	11	(0.2)	12	(0.2)
<i>Diagnostic testing</i>								
Bone scan	223	(4.6)	314	(6.4)	366	(7.5)	486	(10.0)

Table 3

Multivariable models of predictors of treatment in patients with hypercalcemia of malignancy.

	Zoledronic acid or Pamidronate within 48 hours	Calcitonin within 48 hours	Glucocorticoids within 48 hours	Contraindicated drug (lithium or thiazide) within 96 hours
<i>Age</i>				
<50	Referent	Referent	Referent	Referent
50–59	1.03 (0.93–1.14)	0.95 (0.78–1.14)	0.89 (0.71–1.12)	1.72 (0.65–4.53)
60–69	1.04 (0.93–1.15)	0.98 (0.83–1.17)	0.73 (0.58–0.92)*	1.96 (0.72–5.35)
70	0.97 (0.87–1.09)	0.86 (0.71–1.05)	0.67 (0.51–0.88)*	1.87 (0.61–5.69)
<i>Gender</i>				
Male	Referent	Referent	Referent	Referent
Female	0.96 (0.90–1.02)	0.93 (0.82–1.06)	0.90 (0.76–1.06)	1.26 (0.84–1.91)
<i>Year of diagnosis</i>				
2006	Referent	Referent	Referent	Referent
2007	0.97 (0.87–1.07)	0.95 (0.73–1.22)	0.96 (0.76–1.21)	1.24 (0.60–2.59)
2008	0.94 (0.84–1.05)	1.14 (0.90–1.43)	0.82 (0.63–1.06)	1.39 (0.66–2.93)
2009	0.98 (0.88–1.08)	1.15 (0.91–1.45)	0.83 (0.65–1.07)	1.15 (0.55–2.39)
2010	0.97 (0.87–1.08)	1.18 (0.93–1.49)	0.82 (0.64–1.05)	1.09 (0.52–2.30)
2011	0.89 (0.81–0.99)*	1.36 (1.09–1.69)*	0.79 (0.62–1.00)	1.40 (0.65–3.01)
2012	0.90 (0.81–0.99)*	1.43 (1.16–1.76)*	0.82 (0.64–1.05)	1.48 (0.72–3.07)
<i>Race</i>				
White	Referent	Referent	Referent	Referent
Black	1.00 (0.92–1.08)	1.18 (1.03–1.34)*	0.96 (0.81–1.14)	1.29 (0.82–2.03)
Other	1.04 (0.96–1.13)	1.14 (0.97–1.33)	0.81 (0.65–1.00)	0.82 (0.44–1.54)
<i>Marital status</i>				
Married	Referent	Referent	Referent	Referent
Single	1.01 (0.95–1.07)	0.86 (0.77–0.96)*	0.98 (0.86–1.11)	0.87 (0.58–1.31)
Unknown	0.4 (0.84–1.05)	0.87 (0.70–1.07)	1.16 (0.88–1.52)	0.73 (0.37–1.44)
<i>Insurance status</i>				
Commercial	Referent	Referent	Referent	Referent
Medicare	0.96 (0.89–1.03)	0.91 (0.79–1.05)	0.92 (0.76–1.12)	1.66 (0.89–3.09)
Medicaid	1.05 (0.96–1.16)	0.92 (0.75–1.12)	1.14 (0.93–1.41)	1.03 (0.46–2.26)
Uninsured	1.03 (0.91–1.15)	1.04 (0.81–1.33)	0.84 (0.56–1.26)	1.02 (0.33–3.18)
Unknown	0.98 (0.82–1.16)	0.94 (0.63–1.39)	1.34 (0.88–2.03)	3.51 (1.36–9.02)*
<i>Comorbidity</i>				
1	Referent	Referent	Referent	Referent
2	1.45 (0.99–2.12)	0.75 (0.30–1.89)	1.46 (0.51–4.20)	0.80 (0.06–11.51)
3	1.67 (1.19–2.34)*	1.98 (0.95–4.13)	2.67 (1.11–6.42)*	1.89 (0.29–12.33)
<i>Primary tumor site</i>				
Breast	Referent	Referent	Referent	Referent
Lung	1.25 (1.14–1.37)*	1.01 (0.83–1.22)	1.27 (0.99–1.63)	1.00 (0.52–1.91)
Multiple myeloma	1.25 (1.12–1.39)*	1.26 (1.02–1.56)*	2.31 (1.77–3.00)*	1.27 (0.67–2.41)

	Zoledronic acid or Pamidronate within 48 hours	Calcitonin within 48 hours	Glucocorticoids within 48 hours	Contraindicated drug (lithium or thiazide) within 96 hours
Gastrointestinal	1.13 (1.01–1.26)*	0.98 (0.76–1.27)	0.54 (0.37–0.79)*	1.04 (0.50–2.16)
Gynecologic	1.23 (1.08–1.40)*	1.18 (0.88–1.59)	0.87 (0.57–1.31)	0.65 (0.19–2.23)
Genitourinary	1.03 (0.92–1.15)	0.95 (0.76–1.19)	0.87 (0.62–1.21)	1.08 (0.51–2.29)
Other	1.23 (1.09–1.40)*	1.06 (0.81–1.39)	0.75 (0.49–1.15)	0.80 (0.30–2.12)
<i>Area of residence</i>				
Urban	Referent	Referent	Referent	Referent
Rural	0.89 (0.80–0.99)*	1.08 (0.88–1.34)	1.17 (0.95–1.44)	0.61 (0.32–1.19)
<i>Hospital teaching status</i>				
Non-teaching	Referent	Referent	Referent	Referent
Teaching	0.98 (0.91–1.05)	1.11 (0.95–1.31)	1.00 (0.82–1.23)	1.23 (0.84–1.80)
<i>Region</i>				
Northeast	Referent	Referent	Referent	Referent
Midwest	0.91 (0.81–1.02)	0.79 (0.62–1.01)	1.24 (0.97–1.59)	1.19 (0.64–2.22)
South	1.08 (1.00–1.17)*	0.85 (0.72–1.01)	1.01 (0.81–1.25)	1.78 (1.10–2.89)*
West	1.07 (0.97–1.19)	0.95 (0.77–1.17)	1.14 (0.85–1.54)	0.56 (0.26–1.22)
<i>Hospital bed size</i>				
<400	Referent	Referent	Referent	Referent
400–600	0.95 (0.87–1.03)	1.10 (0.91–1.32)	1.06 (0.85–1.32)	0.99 (0.64–1.52)
>600	0.94 (0.84–1.05)	1.22 (0.97–1.53)	1.01 (0.77–1.34)	1.33 (0.81–2.19)
<i>Hospital volume</i>				
Low	Referent	Referent	Referent	Referent
Intermediate	1.03 (0.96–1.12)	0.89 (0.75–1.05)	0.96 (0.79–1.17)	0.89 (0.57–1.40)
High	1.10 (1.00–1.21)*	0.92 (0.75–1.12)	1.25 (0.99–1.57)	0.71 (0.43–1.19)
<i>Attending physician specialty</i>				
Hematology/oncology	Referent	Referent	Referent	Referent
Family practice	0.94 (0.85–1.03)	1.17 (0.93–1.47)	0.54 (0.39–0.73)*	0.86 (0.45–1.66)
Hospitalist	1.03 (0.89–1.20)	1.49 (1.05–2.12)*	0.37 (0.24–0.57)*	0.48 (0.16–1.40)
Other	0.94 (0.88–1.00)	1.21 (1.05–1.41)*	0.64 (0.54–0.76)*	0.87 (0.56–1.34)
<i>Other conditions</i>				
Bone metastasis	1.28 (1.21–1.36)*	1.25 (1.09–1.42)*	1.42 (1.20–1.68)*	1.55 (1.06–2.27)*
Acute renal failure	0.93 (0.87–0.99)*	1.73 (1.52–1.95)	1.00 (0.86–1.16)	1.30 (0.84–2.00)
Chronic renal failure	0.93 (0.87–1.00)	1.06 (0.93–1.20)	0.96 (0.81–1.15)	0.69 (0.41–1.17)
Hypotension	1.10 (0.77–1.57)	1.12 (0.44–2.84)	0.58 (0.30–1.11)	0.59 (0.19–1.84)
Bacteremia	1.11 (0.98–1.25)	1.11 (0.85–1.45)	0.84 (0.55–1.27)	1.13 (0.47–2.75)
Shock	0.98 (0.67–1.42)	0.90 (0.35–2.31)	2.01 (1.05–3.85)*	0.71 (0.23–2.13)
Respiratory failure	1.05 (0.95–1.17)	0.94 (0.75–1.19)	0.91 (0.68–1.22)	1.00 (0.43–2.31)
ICU admission	1.15 (1.08–1.24)*	1.37 (1.18–1.58)*	0.84 (0.67–1.06)	0.94 (0.46–1.92)
Mechanical ventilation	1.01 (0.83–1.23)	0.99 (0.69–1.40)	1.23 (0.76–1.96)	1.76 (0.69–4.54)
<i>Other medications</i>				
Pamidronate or zoledronic acid ^I	-	1.49 (1.33–1.67)*	1.28 (1.12–1.46)*	1.03 (0.71–1.49)
Calcitonin ^I	1.23 (1.16–1.31)*	-	1.39 (1.21–1.60)	0.50 (0.28–0.87)*

	Zoledronic acid or Pamidronate within 48 hours	Calcitonin within 48 hours	Glucocorticoids within 48 hours	Contraindicated drug (lithium or thiazide) within 96 hours
Glucocorticoids ¹	1.11 (1.04–1.18)*	1.34 (1.19–1.51)*	-	1.22 (0.78–1.92)
Contraindicated medications ²	1.03 (0.87–1.21)	0.59 (0.37–0.95)*	1.18 (0.82–1.69)	-

¹ Within 48 hours of admission

² Within 96 hours of admission

Risk ratio (95% confidence interval)

Table 4
Outcomes for propensity score matched cohorts based on receipt of the indicated treatment.

	Prolonged hospitalization		Non-routine discharge		Death	
	OR (95% CI)	Events ^I	OR (95% CI)	Events ^I	OR (95% CI)	Events ^I
Zoledronic acid or pamidronate	0.88 (0.75–1.02)	854	1.09 (0.93–1.27)	846	1.05 (0.80–1.39)	205
Calcitonin	1.12 (0.92–1.35)	577	1.03 (0.84–1.26)	524	1.12 (0.81–1.55)	150
Glucocorticoids	0.88 (0.70–1.11)	379	0.92 (0.73–1.16)	332	1.19 (0.79–1.78)	106

For each primary treatment separate propensity scores were calculated.

^INumber of events for each category in the propensity score