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Case series

Inpatient management of hypercalcemia portends a poor prognosis among gynecologic oncology patients: A trigger to initiate hospice care?

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ABSTRACT

We aim to describe survival outcomes of gynecologic oncology inpatients treated with intravenous bisphosphonates for hypercalcemia and develop a risk stratification model that predicts decreased survival to aid with goals of care discussion. In a single-center, retrospective cohort study of gynecologic oncology patients admitted for bisphosphonate therapy for hypercalcemia. Survival from hypercalcemia to death was assessed by Kaplan-Meier method and log-rank test. Univariate log-rank test and Cox proportional hazards modeling were used to develop a risk stratification model. Sixty-five patients were evaluable with a median follow-up of 83.5 months. Mean age was 59.2 years, 64.6% had recurrent disease, and 30.8% had ≥2 previous lines of chemotherapy. Median survival was 38 days. Our analysis identified four risk factors (RFs) [brain metastasis, > 1 site of metastasis, serum corrected peak calcium > 12.4 (mg/dL), and peak ionized calcium > 5.97 (mg/dL)] that predicted survival and were used to build a risk stratification score. Sum of RFs included 35 patients with 1 RF, 11 had 2 RFs, and 19 had ≥3 RF. Median survival for 1, 2, or ≥ 3 RFs was 53, 28, and 26 days respectively (p = .009). Survival at 6 months was 28.6%, 18.2%, and 5.3% for each group respectively. Hospice enrollment was 26.2%, and did not vary by group (p = .51). Among gynecologic oncology patients, inpatient management of hypercalcemia with bisphosphonates portends poor prognosis. Individualized risk stratification may help guide end-of-life discussions and identify patients who may benefit most from hospice care.

1. Introduction

Hypercalcemia associated with cancer affects up to 30% of oncology patients and portends high morbidity and poor mortality (Stewart, 2005). It may lead to central nervous system disturbances, renal failure, constipation, nausea, and pain (Ralston et al., 1990). These associated findings have been previously studied among cancer patients and reported to occur with a median of 30–55 days prior to death (Ralston et al., 1990; Ling et al., 1995). Hypercalcemia associated with solid tumors is most frequently due to humoral responses caused by parathyroid hormone related protein (PTHrP) secreted by the tumor (Nakayama et al., 1996). PTHrP causes hypercalcemia via enhancing renal retention of calcium and increases bone resorption (Horwitz et al., 2003). First line treatment for hypercalcemia associated with cancer is intravenous (IV) bisphosphonates such as pamidronic or zoledronic acid. These medications will combat the tumor's effects by inhibiting osteoclast bone resorption (Major et al., 2001).

Use of bisphosphonates may effectively decrease a patient's elevated calcium or symptoms. Bisphosphonates may improve breast cancer survival but this finding has not been adequately studied in gynecologic malignancies (Wright et al., 2015; Early Breast Cancer Trialists' Collaborative, G, 2015). Generally, the diagnosis of hypercalcemia is poor prognostic feature that may aid in discussions of goals of care. There is a paucity of data looking at the utilization of specialty palliative care consultation or hospice initiation when patients are found to experience hypercalcemia.

Outcomes of hypercalcemia in women with a gynecologic malignancy has not been well studied and at best, limited to small numbers embedded in published reports that captures oncology patients regardless of primary site (Stewart, 2005; Ralston et al., 1990; Stewart et al., 1982). Our objective was to describe clinical and demographic characteristics of women with a gynecologic malignancy, admitted to an inpatient academic medical center with symptomatic hypercalcemia. Secondary objectives were to determine the prognostic value of hypercalcemia to predict OS and identify subgroups that would benefit most from hospice care.

2. Methods

After receiving approval by the Washington University Human Research Protection office (#201712061), we performed a single-center, retrospective cohort study of women with a gynecologic

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malignancy admitted for inpatient management of hypercalcemia between 9/1/2012-10/1/2017. Our cohort was identified by querying the inpatient pharmacy records of intravenous (IV) pamidronic or zoledronic acid administration. Patients were included if they met the following criteria: 1) admitted to the gynecologic oncology service with a confirmed gynecologic malignancy of any stage or type, 2) had a serum calcium or serum albumin-corrected calcium level of 10.2 mg/dL or higher, and 3) received IV pamidronic or zoledronic acid. The calculation of albumin-corrected calcium = Serum calcium $+0.8*(4\ \text{g/dL}-\text{patient's albumin g/dL})$. All patients were considered to have symptomatic hypercalcemia but severity of symptoms was not quantified. No patients were readmitted and no patient was accounted in our analysis more than once.

Survival was assessed by Kaplan-Meier method and log-rank test. OS was calculated from date of hypercalcemia to date of expiration. We performed univariate analysis with the log-rank test to identify clinical and demographic factors that predicted decreased survival. Those risk factors found to be statistically significant (eg, presence of brain metastasis and > 1 site of metastasis; $p < .05$) were then adjusted for in our Cox proportional hazard regression model to identify a predictive serum markers (eg, albumin-corrected peak calcium, peak ionized calcium, and albumin) to be used in our risk stratification model. Median lab values of > 5.9 mg/dL for ionized calcium and > 12.4 mg/dL for serum corrected calcium were used as cutoffs to ensure adequate sample size for analysis. Lastly both ionized calcium and serum corrected calcium were included as 20 patients did not have an ionized calcium measured during their hospitalization.

Four significant factors from both univariate and multivariate analyses (presence of brain metastasis, > 1 site of metastasis, ionized calcium > 5.9 mg/dL, and serum corrected calcium > 12.4 mg/dL), were used to build a prognostic risk stratification system. Scores were determined by the sum of predictive variables with a possible maximum score of 4. Median survivals of patients with score 0, 1, 2, and ≥3 were determined with Kaplan-Meier method and compared using log-rank test. *P*-values ≤.05 were considered statistically significant. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

3. Results

We identified 1260 patients who received IV pamidronic or zoledronic acid during the study period. Gynecologic malignancy occurred in 116 patients, and 51 were excluded secondary to normal calcium levels. Therefore, 65 patients were included in this analysis and of these, 55 were deceased at last follow-up, and 10 were long-term survivors with median follow-up of 83.5 months from diagnosis of hypercalcemia.

The mean age was 59.2 years old, most were white (73.9%) and privately insured (41.5%). Disease site origin was heterogenous with 35.4% uterine, 29.2% ovarian, and 24.6% cervical. The most frequent histologies were squamous (29.2%), adenocarcinoma (21.5%), and serous (16.9%). The majority of patients at time of inpatient admission had 2 or more sites of metastatic disease (89%), the most common locations included abdomen (89.2%), bone (49.2%), lung (36.9%), liver (33.9%), and brain (6.2%). More than half suffered from recurrent disease (64.6%) and 30.8% had 2 or more previous lines of chemotherapy (Table 1).

Details of hospital admission are summarized in Table 2. Most patients were admitted for < 7 days (55.4%). Admission diagnoses beyond hypercalcemia included pain (46.2%), inanition "failure to thrive" (20.0%), nausea (18.5%), and underlying infectious process (13.9%). The severity of hypercalcemia also varied; median serum corrected peak calcium levels 12.4 mg/dL (range, 10.2–18.5), and median serum peak ionized calcium levels 5.97 mg/dL (range, 3.5–8.9). The majority of patients demonstrated signs of protein calorie malnutrition with 75.4% having a serum albumin < 3.5 g/dL. During admission, 73.9% received specialty palliative care consultation, and 26.2% were discharged with hospice services.

Table 1
Clinicodemographic features.

	Mean	
Age	59.2 years	
BMI	27.5 kg/m^2	
	N	%
Race		
White	48	73.9%
African American	14	21.5%
Asian	1	1.5%
Hispanic	1	1.5%
Other	1	1.5%
Insurance		
Private	27	41.5%
Medicaid	9	13.9%
Medicare	27	41.5%
Self-pay	2	3.1%
Disease site		
Ovary	19	29.2%
Uterus	23	35.4%
Cervix	16	24.6%
Other	7	10.7%
Histology		
Adenocarcinoma	14	21.5%
Squamous	19	29.2%
Serous	11	16.9%
Clear cell	5	7.7%
Carcinosarcoma	5	7.7%
Neuroendocrine	4	6.2%
Other	7	10.8%
Initial stage		
I	5	7.7%
II	6	9.2%
III	25	38.5%
IV	29	44.6%
Cancer setting		
Primary	23	35.4%
Recurrent	42	64.6%
Previous lines of chemotherapy		
0	26	40.0%
1	19	39.2%
2	10	15.4%
≥3	10	15.4%
Sum of metastatic sites		
1	7	10.8%
2	18	27.7%
3	24	36.9%
≥4	16	24.6%
Location of metastasis		
Abdomen	58	89.2%
Bone	32	49.2%
Lung	24	36.9%
Liver	22	33.9%
Brain	4	6.2%

Median OS for the entire cohort was 38 days (Fig. 1). Univariate analysis revealed that presence of brain metastasis (compared to no brain metastasis) and > 1 metastatic site (versus 1 metastatic site) were associated with a statistically significant decrease in OS (Table 3). After adjusting for both of these variables in our Cox regression model, serum corrected peak calcium > 12.4 (mg/dL), and peak ionized calcium > 5.97 (mg/dL) were associated with worse median survival (aHR 1.88, 95% CI 1.1–3.3; and aHR 2.43, 95% CI 1.26–4.68 respectively).

Next we identified subgroups based upon a risk factor (RF) stratification system to predict OS. Stratified by number of RFs present (1, 2 or ≥3 among brain metastasis, > 1 site of metastasis, serum ionized calcium > 5.9 mg/dL, and serum corrected calcium > 12.4 mg/dL), 35 patients had 1 RF, 11 had 2 RFs, and 19 had ≥3 RF. Median survival for

Table 2
Admission details.

	N	%
Hospital duration		
< 7 days	36	55.4%
≥7 days	29	44.6%
Admission diagnosis		
Pain	30	46.2%
Inanition ("Failure to thrive")	13	20.0%
Nausea	12	18.5%
Infection	9	13.9%
Renal failure	7	10.8%
Anemia	7	10.8%
VTE/PE	6	9.2%
Bowel obstruction	2	3.1%
Other	9	13.9%
Peak serum corrected calcium		
> 12.4	31	47.7%
≤ 12.4	34	52.3%
Peak ionized calcium[a]		
> 5.97	21	32.3%
≤5.97	24	36.9%
Admission albumin		
> 3.5	16	24.6%
≤3.5	49	75.4%
In hospital death		
Yes	19	29.2%
No	46	70.8%
Specialty palliative care consult		
Yes	48	73.85%
No	17	26.15%
Discharge location		
Home	40	61.5%
Hospice	17	26.2%
SNF	8	12.3%
Readmission within 30 days		
Yes	27	41.5%
No	38	58.5%

[a] N of 45.

1, 2, or ≥3 RFs was 53, 28, and 26 days respectively (Fig. 2, log-rank p = .009). Survival at 6 months was 28.6%, 18.2%, and 5.3% for each risk group respectively. Despite a significant increase in specialty palliative care services from 60% in those with 1 RF to 94.7% with ≥3RF (p = .017), there was no difference in hospice enrollment by RF (p = .51). Of the 17 hospice enrollees, 8 had 1RF, 2 had 2RF, and 7 had ≥3RF.

Adjuvant chemotherapy was delivered to 18 patients and 7 (38.9%) were treated within the last 30 days of life. However there were 6 patients with durable responses (304–1994 days), all of whom had only 1 RF.

4. Discussion

Our findings suggest hypercalcemia associated with gynecologic cancers portends a poor prognosis and when additional RFs are present (eg, brain metastasis, > 1 site of metastasis, ionized calcium ≥5.9 mg/dL, and serum corrected calcium ≥12.4 mg/dL) should prompt discussions regarding goals of care with consideration of focusing on palliation of symptoms and hospice enrollment. Our cohort's median survival was only 38 days which is considerably less than that reported by Penel et al. (Ralston et al., 1990; Penel et al., 2008) and Ralston et al. (Ralston et al., 1990; Penel et al., 2008) of 64 and 126 days, respectively. The most striking difference which can account for such discrepancy is our inpatient admission criteria as compared to the prior studies which focused on the outpatient setting.

Adding to the literature on hypercalcemia, we were able to demonstrate a risk stratification system among gynecologic oncology inpatients that correlates increasing number of RFs (eg, brain metastasis), > 1 site of metastasis, serum corrected peak calcium > 12.4 mg/dL, and peak ionized calcium > 5.97 mg/dL with worse OS. This is consistent with a prior study by Penel et al. (Penel et al., 2008; Penel et al., 2009) that included 260 oncology patients, of which 10.7% had a confirmed gynecologic malignancy. They showed a similar survival trend based on a three-tier risk stratification system based on four independent predicting factors: serum-corrected calcium > 2.83 mol/L, albuminemia < 35 g/L, squamous cell cancer type, and presence of liver or bone metastases (Penel et al., 2008). Unlike other studies however, we did not detect a significant difference in women with primary versus recurrent disease status (58 and 33 days, p = .2) Nor did we find a significant association between OS and presence of visceral mets as demonstrated in other non-gynecologic cancers (de Wit &

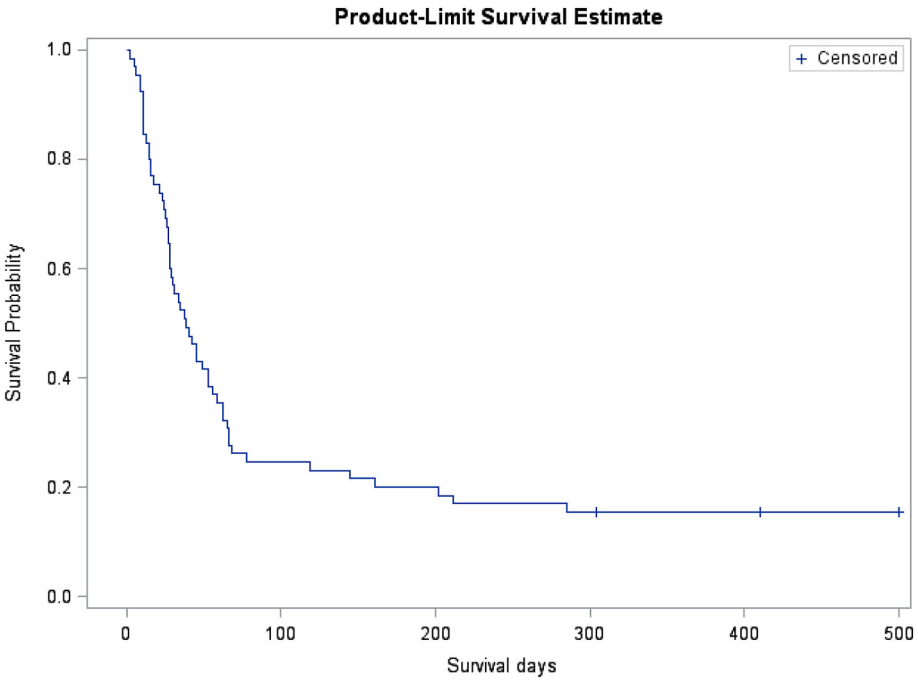

Fig. 1. Overall survival. Median survival for entire cohort was 38 days (95%CI: 28–56, range: 2–1994).

Table 3
Univariate analysis.

	Median survival (days)	95% CI (days)	*p* value (log-rank)
Age			
< 65	49	(29, 62)	0.23
≥65	28	(13, 45)	
BMI			
< 30	37	(26, 58)	0.57
30–39.9	42	(9, 211)	
≥ 40	30	(28, 161)	
Race			
White	41	(28, 62)	0.43
African American	29	(15, 53)	
Other	38	(21, 66)	
Disease site			
Ovary	30	(13, 66)	0.84
Uterus	49	(28, 78)	
Cervix	30	(21, 68)	
Other	37	(2,53)	
Histology			
Adenocarcinoma	31	(11, 161)	0.68
Squamous	38	(24, 56)	
Other	47	(28, 66)	
Cancer Setting			
Primary	58	(25, 119)	0.20
Recurrent	33	(27, 45)	
Previous lines of chemo			
0	43	(25, 65)	0.77
1	42	(21, 161)	
2	33	(9, 53)	
≥ 3	39	(6, 66)	
Sum of metastatic sites			
1	304	NA	**0.01**
2	64	(28, 68)	
3	39	(17, 56)	
≥ 4	25	(11, 45)	
Bone metastasis			
Presence	42	(21, 62)	0.47
Absence	37	(28, 62)	
Lung metastasis			
Presence	30	(14, 53)	0.15
Absence	42	(28, 66)	
Brain metastasis			
Presence	22	(15, 27)	**0.01**
Absence	42	(29, 58)	
Liver metastasis			
Presence	30	(17, 62)	0.15
Absence	42	(28, 62)	
Abdomen metastasis			
Presence	35	(27, 53)	0.23
Absence	65	(11, NA)	

NA: not able to calculate 95% CI.

Cleton, 1994; Truong et al., 2003).

The presence of multiple RFs correlated with specialty palliative care consultation, but not hospice enrollment. The prognostic value of our proposed risk stratification system to predict mortality among gynecologic oncology patients highlights the potential for a practical and objective tool to aid providers in the discussion of goals of care and if appropriate, initiation of hospice. Considering Medicare eligibility criteria for hospice includes documentation of a terminal illness with a prognosis of six months or less, the four independent factors used in our risk stratification contribute distinct survival curves with relevant time intervals based on the number of RFs present. These findings should be replicated in a larger dataset before integrating the presence of hypercalcemia into clinical decision making at the end of life, but if confirmed may aid in avoiding futile treatments and allow for emphasis on management strategies that optimize quality of life.

Strengths of our study revolve around our unique study population and volume. Given our wide referral base as academic institution with an affiliated cancer center, our study represents one of the largest publications to date regarding hypercalcemia in gynecologic malignancies. Although only 65 women were studied, we were able to stratify prognosis based on the risk factors. Previous data frequently include a heterogenous group of oncology patients with minimal to no gynecologic representation. Nonetheless, we acknowledge limitations posed by the infrequent incidence of hypercalcemia in gynecologic oncology patients. Limitation include underpowered analysis to compare survival outcomes between staged-matched patients with and without hypercalcemia. Additionally, we were unable to control for performance status, serum level of PTHrP, or other confounding comorbidities. Our data does shed light on the prognostic value of inpatient management of hypercalcemia and consideration to initiate conversations regarding hospice care in the highest risk patients. We acknowledge that our results may not apply to patients in the outpatient setting.

In conclusion, our data affirm the poor prognostic value of inpatient management of hypercalcemia associated with gynecologic malignancies. Individualized risk stratification based on four clinical RFs—brain metastasis, > 1 site of metastasis, serum corrected peak calcium > 12.4 mg/dL, and peak ionized calcium > 5.97 (mg/dL), suggest that patients of high risk may benefit from end-of-life decision making and appropriately identify patients who may benefit from hospice care.

Conflict of interest

The authors declare no potential conflict of interest.

Disclosures

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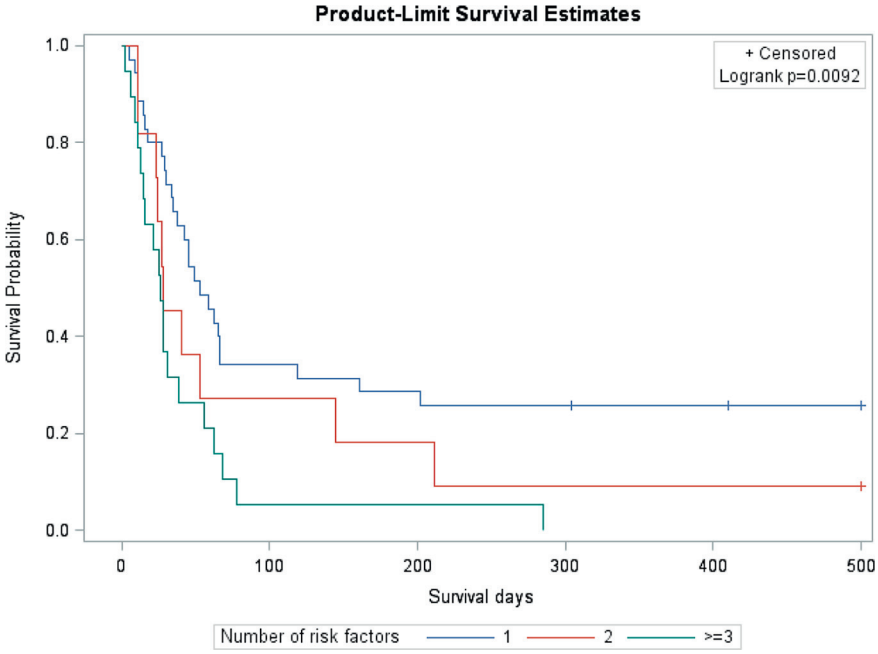
Author contributions

1. J.C. Cripe, M.D.: Lead author who designed the study, performed the majority of data collection and entry, and assisted with manuscript writing and editing.
2. T.R. Buchanan, M.D.: Assisted with manuscript writing and revisions.
3. L. Wan, M.P·H: Assisted with statistical analysis and approval of final submitted version.
4. AR Hagemann, M.D., M.S.C·I: Assisted with manuscript revisions and approval of final submitted version.
5. C.K. McCourt, M.D.: Assisted with manuscript revisions and approval of final submitted version.
6. L.S. Massad, M.D.: Assisted with manuscript revisions and approval of final submitted version
7. K.C. Fuh, M.D., Ph.D.: Assisted with manuscript revisions and approval of final submitted version.
8. D.G. Mutch, M.D.: Assisted with manuscript revisions and approval of final submitted version.
9. M.A. Powell, M.D.: Assisted with manuscript revisions and approval of final submitted version.
10. P.H. Thaker, M.D., M.S.: Assisted with manuscript revisions and approval of final submitted version.
11. L.M. Kuroki, M.D., M.S.C·I: Senior author who helped with initial design, and manuscript writing and editing.



	Median survival days (95%CI)	Crude HR (95% CI)
Number of risk factors		
1	53 (35, 66)	0.41 (0.22, 0.74)
2	28 (11, 144)	0.65 (0.30, 1.41)
≥3	26 (13, 38)	Reference

Fig. 2. Overall survival risk stratification. Sum of risk factors = (> 1 metastatic lesion, Brain metastasis, elevated ionized calcium, elevated peak calcium).

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.gore.2019.01.005.

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