Hypercalcemia in advanced cholangiocarcinoma

Eirini Konstantinidou[1], Jordan R. Maurer[2], Jennifer R. Stanton[2], Islam Baiev[2], Joseph Franses[2], Ryan D Nipp[2], Lawrence S Blaszkowsky[2], Jon Dubois[2], Bruce J Giantonio[2], Eric J Roeland[2], Jennifer Y Wo[2], Samuel J Klempner[2], Aparna R Parikh[2], Colin D Weekes[2], Theodore S Hong[2], Jill N Allen[2], Ryan B Corcoran[2], David P Ryan[2], Jeffrey W Clark[2], Andrew X Zhu[2], Lipika Goyal[2]

[1]Beth Israel Deaconess Medical Center, Boston, MA, [2]Massachusetts General Hospital Cancer Center, Boston, MA,

BACKGROUND

Hypercalcemia is a serious metabolic complications of malignancy, occurring in 5% to 30% of patients with cancer during the course of their disease.[1,2] Hypercalcemia of malignancy arises via four mechanisms including excessive secretion of parathyroid hormone-related protein, local osteolytic hypercalcemia caused by bone metastases, tumoral production of 1,25-dihydroxyvitamin D and ectopic secretion of parathyroid hormone.[3] In hepatocellular carcinoma and esophageal cancer, hypercalcemia of malignancy is associated with a poor prognosis.[4,5] However, it has not been well studied in cholangiocarcinoma as data is limited to case reports and small case series.[6,7] We present the largest study of hypercalcemia in cholangiocarcinoma.

OBJECTIVES

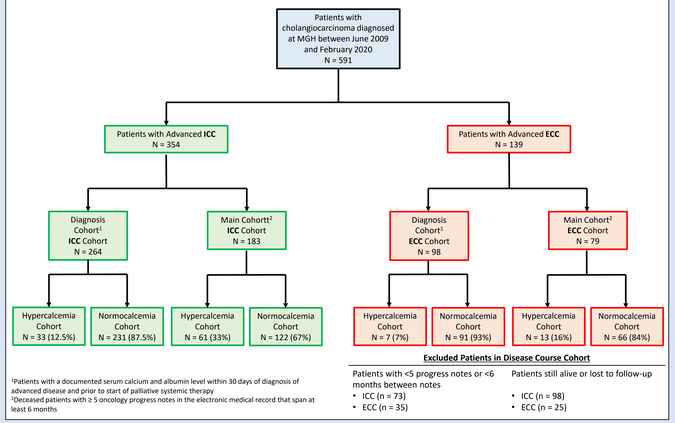
In this study we aimed to evaluate the prevalence of hypercalcemia in patients diagnosed with advanced cholangiocarcinoma both at time of diagnosis and during their disease course. We also aimed to characterize the clinical phenotype, genomic associations and prognostic implications of hypercalcemia in cholangiocarcinoma.

MATERIALS AND METHODS

Patients with histologically confirmed, advanced cholangiocarcinoma were identified from the Massachusetts General Hospital (MGH) tumor registry and tumor biobanking protocol. Patients with at least five calcium and albumin values over at least six months were included in our Main Cohort. Patients with documented serum albumin and calcium levels within 30 days of the date of diagnosis of advanced disease were included in the Diagnosis Cohort. Hypercalcemia was defined as albumin-corrected calcium level ≥10.5 mg/dL. Patients with at least one documented hypercalcemia event were included in the "Hypercalcemia Cohort", while patients without a documented hypercalcemia event were included in the "Normocalcemia Cohort".

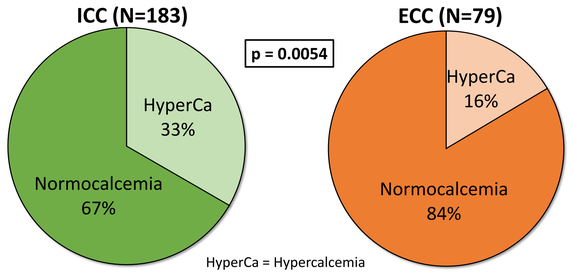
RESULTS

Figure 1. Patient enrollment summary to study



RESULTS

Figure 2. Prevalence of hypercalcemia in patients with intrahepatic cholangiocarcinoma (ICC) and extrahepatic cholangiocarcinoma (ECC)



HyperCa = Hypercalcemia

Table 1. Baseline characteristics of patients diagnosed with ICC

Characteristic	Hypercalcemia N=61 N (%)	Normocalcemia N=122 N (%)	P Value
Age at Initial Diagnosis			
Median (Range)	65.3 (22.5 – 88.8)	63.7 (29.4 - 91.9)	p = 0.7316
Gender			
Male	30 (49%)	56 (46%)	p = 0.6753
Female	31 (51%)	66 (54%)	
Initial Presentation			
Resectable	7 (11%)	22 (18%)	***p = 0.0328***
Locally Advanced	6 (10%)	23 (19%)	
Primary Metastatic	48 (79%)	77 (63%)	
Number of Sites of Distant Metastases at Advanced Diagnosis of Disease			
<3	41 (67%)	103 (84%)	***p = 0.0128***
≥3	20 (33%)	19 (16%)	
Tumor Differentiation			
Well	3/34 (9%)	1/78 (1%)	P Value for Poor Differentiation: **0.1677**
Well to Moderately	1/34 (3%)	3/78 (4%)	
Moderately	11/34 (32%)	38/78 (49%)	
Moderately to Poor	3/34 (9%)	10/78 (13%)	
Poor	16/34 (47%)	26/78 (33%)	
Unknown	27/61 (44%)	44/122 (36%)	NE

Figure 3. Frequency of genetic alterations in patients with ICC

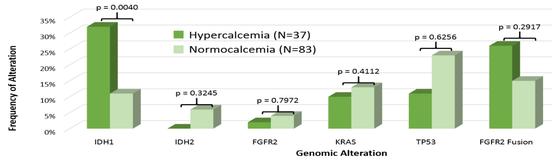


Table 2. Baseline characteristics of patients diagnosed with ECC

Characteristic	Hypercalcemia N=13 N (%)	Normocalcemia N=66 N (%)	P Value
Age at Initial Diagnosis			
Median (Range)	63.2 (35.0 – 93.9)	65.2 (33.1 - 89.0)	p = 0.6892
Gender			
Male	8 (62%)	46 (70%)	p = 0.5632
Female	5 (28%)	20 (30%)	
Initial Presentation			
Resectable	4 (36%)	36 (55%)	p = 0.4356
Locally Advanced	5 (38%)	19 (28%)	
Primary Metastatic	4 (36%)	11 (17%)	
Number of Sites of Distant Metastases at Advanced Diagnosis of Disease			
<3	11 (84%)	65 (98%)	***p = 0.0168***
≥3	2 (16%)	1 (2%)	
Tumor Differentiation			
Well	0/5 (0%)	3/44 (7%)	P Value for Poor Differentiation: **0.0115**
Well to Moderately	0/5 (0%)	0/44 (0%)	
Moderately	1/5 (20%)	22/44 (50%)	
Moderately to Poor	0/5 (0%)	8/44 (18%)	
Poor	4/5 (80%)	11/44 (25%)	
Unknown	8/13 (62%)	22/66 (33%)	NE

Table 3. Hypercalcemia in cholangiocarcinoma ICC vs ECC

Characteristic	ICC N=61 N (%)	ECC N=13 N (%)	P Value
Use of Bisphosphonates to Treat Hypercalcemia			
Yes	17 (28%)	0 (0%)	***p = 0.0312***
No	44 (72%)	13 (100%)	
Presence of Bone Metastases at First Hypercalcemia Event			
Yes	19 (31%)	0 (0%)	***p = 0.0167***
No	42 (66%)	13 (100%)	
Frequency of Grade 3 or 4 Hypercalcemia by CTCAE v5.0			
Grade 3 or 4	10 (16%)	1 (8%)	p = 0.4233
Overall Survival from First Instance of Hypercalcemia (Months)			
Median (months)	4.43	1.77	***p = 0.0312***

Figure 4. Overall survival amongst patients with IDH1 mutant ICC who developed hypercalcemia vs. normocalcemia

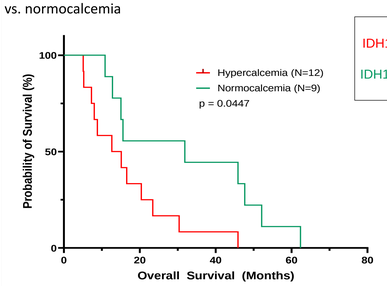
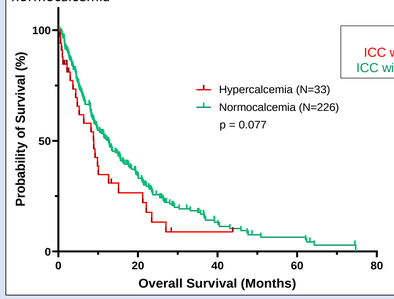


Figure 5. Overall survival amongst patients with ICC who presented with hypercalcemia vs. normocalcemia



CONCLUSIONS

- Hypercalcemia is a **common** complication of cholangiocarcinoma affecting 33% of patients with ICC and 16% of patients with ECC
- Hypercalcemia is associated with **high burden of metastatic disease**
- Hypercalcemia is associated with **IDH1 mutant disease** in ICC
- Hypercalcemia is associated with **poor tumor differentiation** in ECC but the number of patients is small and requires further validation
- Patients with ICC more frequently develop **bone metastases** and are more frequently treated with **bisphosphonates** compared to patients with ECC
- Patients with IDH1 mutant ICC who develop hypercalcemia had a trend towards a **shorter median survival** compared to patients with normocalcemia.

ACKNOWLEDGEMENTS

We are extremely grateful to the patients and their families for their participation in this study. We would also like to thank and acknowledge the research personnel and collaborating physicians who aided in this study.

References

1. Stewart AF. Clinical practice. Hypercalcemia associated with cancer. N Engl J Med. 2005;352(4):373-379
2. Lumachi F, Brunello A, Roma A, Basso U. Cancer-induced hypercalcemia. Anticancer Res. 2009;29(5):1551-1555.
3. Mirrakhimov AE. Hypercalcemia of Malignancy: An Update on Pathogenesis and Management. N Am J Med Sci. 2015;7(11):483-493.
4. Chang PE, Ong WC, Lui HF, Tan CK. Epidemiology and prognosis of paraneoplastic syndromes in hepatocellular carcinoma. ISRN Oncol. 2013 Dec 11;2013:684026
5. Kuwano H, Baba H, Matsuda H, et al. Hypercalcemia related to the poor prognosis of patients with squamous cell carcinoma of the esophagus. J Surg Oncol. 1989 Dec;42(4):229-33.
6. Erdinc B, Ramachandran P, Yadav R, Sahni S, Joseph G. Cholangiocarcinoma Presenting as Humoral Hypercalcemia of Malignancy: A Case Report and Literature Review. Cureus. 2019 Dec 27;11(12)
7. Meegada S, Eisen R, Coons G, Verma R. Intrahepatic Cholangiocarcinoma Associated with High Procalcitonin, Hypercalcemia, Polycythemia and Leukocytosis. Cureus. 2020 Jan 7;12(1)

AMMF's 2021 European Cholangiocarcinoma Conference