Brief Report

Association Between Plasma Brain Natriuretic Peptide and Overall Survival in Patients With Advanced Cancer: Preliminary Findings

David Hui, MD, MSc, Jane Naberhuis, PhD, Seyedeh Dibaj, PhD, Mujtaba Naqvi, MD, Diane Liu, MS, and Eduardo Bruera, MD

Department of Palliative Care (D.H., J.N., M.N., E.B.), Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center; and Department of Biostatistics (S.D., D.L.), The University of Texas MD Anderson Cancer Center, Houston, Texas, USA

Abstract

Context. Atrial and brain natriuretic peptides (ANP and BNP) are established diagnostic and prognostic markers in heart failure, but their utility in patients with advanced cancer is unclear.

Objectives. Our objective was to examine the association between plasma natriuretic peptides and survival in patients with advanced cancer without clinical evidence of heart failure.

Methods. This exploratory analysis of a multicenter, randomized clinical trial of cancer patients receiving hospice care assessed the association between elevated plasma ANP, BNP, or Pro-BNP (cutoffs of >77, 100, and 900 pg/mL, respectively) and overall survival. Time-to-event analyses, including multivariate Cox regression, were conducted.

Results. Among 97 patients, the mean age was 67.2 years and the overall survival was 16 days (95% CI, 13−23 days). ANP, BNP, and Pro-BNP were elevated in 29 of 36 (81%), nine of 23 (39%), and 32 of 38 (84%) patients, respectively. Elevated ANP, BNP, or Pro-BNP was associated with worse survival (median 14 vs. 21 days; $P = 0.02$). BNP or Pro-BNP was inversely associated with overall survival (hazard ratio = 2.27; 95% CI, 1.29−3.97) in univariate Cox regression analysis, and remained significant in multivariate Cox regression analysis (hazard ratio = 3.09; 95% CI, 1.40−6.84) after adjusting for treatment group and known prognostic variables such as performance status, albumin, creatinine, delirium, dyspnea, and anorexia. Elevated ANP alone was not significantly associated with survival ($P = 0.17$).

Conclusion. Our preliminary findings suggest that BNP or Pro-BNP may be a novel objective prognostic marker in cancer patients without heart failure. Further research is needed to confirm these findings. J Pain Symptom Manage 2019;58:465−471.

Key Words

Atrial natriuretic factor, natriuretic peptide, brain, neoplasms, palliative care, prognosis

Introduction

Global annual deaths from cancer are projected to nearly double in the next two decades, from 9.6 million in 2018 to 16.4 million in 2040.[1] As patients approach the last weeks of life, they and their families are faced with many important decisions, such as whether to pursue further cancer treatments and when to say goodbye. The ability to accurately predict survival in patients with advanced cancer would help clinicians personalize care, particularly in the last weeks of life when many complex decisions are based on prognosis.[2] However, few objective prognostic markers are available in this setting.

Released from the atria and ventricles of the heart, respectively, atrial and brain natriuretic peptides (ANP and BNP) are highly sensitive indicators of intravenous volume that exert diuretic, natriuretic,

Address correspondence to: David Hui, MD, MSc, Department of Palliative Care, Rehabilitation and Integrative Medicine, The University of Texas MD Anderson Cancer Center, 1515 Holcombe Blvd., Unit 1414, Houston, TX 77030, USA. E-mail: dhui@mdanderson.org

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and hypotensive effects.[3,4] The prognostic utility of ANP and BNP are well established in heart and renal failure,[5,6] and have also been demonstrated in acute coronary syndrome and stable angina,[5,7–9] as well as in hypertensive[10,11] and septic patients.[12]

Studies of the prognostic utility of ANP or BNP in cancer have typically been limited to patients with specific treatment-related cardiotoxicity,[13] and none have focused on the last weeks of life. Additional insight regarding release of ANP, BNP, and its precursor Pro-BNP in the last weeks of life may provide fundamental insights into the physiologic changes that occur during the dying process and provide an objective prognostic marker. We hypothesized that cardiac function is impaired during the final weeks of life, which may be detected by changes in natriuretic peptide levels. Using data collected from a multicenter, randomized clinical trial that examined the impact of parenteral hydration in patients with advanced cancer enrolled under hospice and without clinical heart failure,[14] we conducted a post hoc analysis to examine the association of ANP, BNP, and Pro-BNP with overall survival.

Methods

Patients

The present analysis used data from a previously reported, multicenter, double-blind, randomized clinical trial (ClinicalTrials.gov identifier NCT00423722) that assessed the effect of hydration on symptoms associated with dehydration in patients with advanced cancer enrolled under hospice care.[14] Patients were recruited from five home hospice agencies in the Greater Houston area, including Christus VNA Hospice, Houston Hospice, Odyssey Hospice, Silverado Hospice, and Vitas Hospice between February 2007 and April 2011. Eligibility criteria were as previously reported.[14] Briefly, inclusion criteria were patients with advanced cancer (i.e., locally recurrent or metastatic disease), age ≥ 18 years, with life expectancy ≥ one week, and evidence of mild/moderate dehydration (Dehydration Assessment Scale score ≥ 2 on a seven-point scale and decreased subclavicular skin turgor) and oral fluid intake < 1000 mL/d. Patients were excluded if they had Memorial Delirium Assessment Scale (MDAS) score ≥13, a history or clinical evidence of congestive heart failure or renal failure with creatinine >2.25 mg/dL, or a history of bleeding disorders or severe dehydration (no urine output for 12 hours or decreased blood pressure, limb perfusion, or consciousness). The institutional review board at MD Anderson Cancer Center approved the study. All patients provided written informed consent.

Study Design and Interventions

Patients were randomized in a 1:1 ratio to receive subcutaneous hydration (1000 mL normal saline/d) or control (100 mL normal saline/d) over four hours until she/he became unresponsive, developed progressive coma, or died.[14] The primary outcome was change in the sum of four dehydration symptoms (fatigue, myoclonus, sedation, and hallucinations) between 4th day and baseline.

Data Collection

For the present analysis, 10 mL of blood was collected at baseline, centrifuged, and immediately analyzed for plasma albumin, creatinine, and natriuretic peptides (ADVIA Centaur CP Immunoassay System; Siemens Healthcare, Munich, Germany). Plasma BNP quantification was ordered for all specimens. However, because of modifications in clinical laboratory procedures during the study, only a subset of samples were analyzed for BNP. The remaining samples were analyzed for either ANP or Pro-BNP. Survival data were extracted from the medical record. Overall survival was defined as time from study enrollment to date of last follow-up or death.

Statistical Analysis

The present exploratory analysis assessed demographic, clinical, and biochemical data as well as overall survival from enrollment.[14] Elevations in natriuretic peptide concentrations were defined according to published criteria for acutely decompensated heart failure as >100 and 900 pg/mL for BNP and Pro-BNP, respectively.[15] As no clear diagnostic cut-off has been established for ANP, elevated ANP was defined as per the laboratory upper limit of >77 pg/mL.[16] Given these multiple cut-off criteria, patients were dichotomized into either normal or elevated ANP, BNP, or Pro-BNP. The subgroup in which BNP or Pro-BNP was measured was also examined. Association between elevated BNP or Pro-BNP and other prognostic variables were assessed using the Wilcoxon rank sum test, chi-squared test, or Fisher exact test. Kaplan-Meier estimates of overall survival were plotted against time. Log-rank test was used to evaluate the association between elevated natriuretic peptides and overall survival. Univariate Cox proportional hazard regression was fitted to evaluate the association of demographic and clinical characteristics as well as elevated BNP with overall survival. In addition to the study group (hydration vs. control), age, sex, performance status, MDAS, anorexia, dyspnea, albumin, and creatinine were analyzed at the time of enrollment and included as covariates in a multivariable Cox proportional hazard model. A two-sided *P*-value of <0.05 was considered statistically significant. All

analyses were conducted using SAS 9.4 software (SAS Institute, Cary, NC).

Results

Demographics

Demographics and baseline characteristics of patients ($N = 97$) are shown in Table 1. Patients' mean age was 67.2 years (range 38.0–92.0 years). Men (56.7%) and women were similarly represented, and 62.9% of patients were white. The most commonly observed cancers included gastrointestinal (35.1%), lung (22.7%), and genitourinary (15.5%). The overall survival was 16 days (95% CI, 13–23 days). Most patients had an Eastern Cooperative Oncology Group performance status of 3 (51 of 96; 53%) or 4 (35 of 96; 37%). Natriuretic peptides ANP, BNP, and Pro-BNP were elevated in 29 of 36 (81%), nine of 23 (39%), and 32 of 38 (84%) patients in which they were measured, respectively. There were no differences in plasma ANP, BNP, or Pro-BNP concentrations between the hydration and control groups.

Association Between Elevated Natriuretic Peptides and Survival

Elevated plasma ANP, BNP, or Pro-BNP (Fig. 1A) and elevated BNP or Pro-BNP (Fig. 1B) were significantly associated with worse survival; elevated plasma ANP alone (Fig. 1C) was not. Median overall survival was 21 days (95% CI, 12–34 days) in patients with normal BNP or Pro-BNP, and 13 days (95% CI, 7–16 days) in patients with elevated BNP or Pro-BNP (Table 2). Accordingly, subsequent analyses were focused on patients in whom BNP or Pro-BNP was measured.

Univariate Cox proportional regression model indicated significant association between elevated plasma BNP or Pro-BNP and overall survival (hazard ratio 2.27 [95% CI, 1.29–3.97]; $P = 0.004$; Table 3). After adjusting for baseline variables, elevated BNP or Pro-BNP remained significant in multivariate Cox proportional hazard regression model (hazard ratio 3.09 [95% CI, 1.40–6.84]; $P = 0.005$; Table 3).

Association Between Elevated BNP and Other Prognostic Variables

Plasma creatinine was significantly higher in patients with elevated BNP or Pro-BNP (1.2 ± 0.5 mg/dL vs. 0.9 ± 0.4 mg/dL; $P = 0.008$). Elevated BNP or Pro-BNP was not associated with age, sex, race, cancer type, Eastern Cooperative Oncology Group performance status, Edmonton Symptom Assessment Scale symptom scores, MDAS, albumin, dehydration scores, intervention group, or myoclonus jerks.

Table 1
Baseline Patient Characteristics

Characteristic	Plasma Natriuretic peptide[a] ANP ($n = 36$)	Plasma Natriuretic peptide[a] BNP or Pro-BNP ($n = 61$)
Age, mean (range), yrs	66.8 (41.0, 91.0)	67.5 (38, 92.0)
Gender, no. (%)		
Female	15 (42)	27 (44)
Male	21 (58)	34 (56)
Race, no. (%)		
White	20 (56)	41 (67)
Black	11 (31)	13 (21)
Hispanic	5 (14)	6 (10)
Other	0 (0)	1 (2)
Cancer type, no. (%)		
Breast	1 (3)	1 (2)
Gastrointestinal	12 (33)	22 (36)
Genitourinary	3 (8)	12 (20)
Gynecologic	3 (8)	3 (5)
Head & neck	1 (3)	3 (5)
Hematological	1 (3)	2 (3)
Lung	9 (25)	13 (21)
Other	6 (17)	5 (8)
ECOG, no. (%)[b]		
2	2 (6)	8 (13)
3	16 (44)	35 (58)
4	18 (50)	17 (28)
MDAS, mean ± SD	5.60 ± 3.72	5.78 ± 3.52
Appetite, mean ± SD, ESAS	7.03 ± 2.31	6.87 ± 2.72
Albumin, mean ± SD, g/dL	2.69 ± .55	3.02 ± .57

ANP = atrial natriuretic peptide; BNP = brain natriuretic peptide; ECOG = Eastern Cooperative Oncology Group performance status; MDAS = Memorial Delirium Assessment Scale; ESAS = Edmonton Symptom Assessment Scale.
[a]Percentages have been rounded and may not total 100.
[b]Higher scores indicate worse performance status.

Discussion

In this secondary analysis of a randomized controlled trial of cancer patients without clinical evidence of heart failure, elevated plasma BNP or Pro-BNP was significantly inversely associated with overall survival in multivariate analysis after adjusting for known prognostic variables. Elevated BNP or Pro-BNP may indicate the presence of cardiac dysfunction within the last weeks of life. This study may have important implications for understanding physiologic changes in the last weeks of life, as well as for the utility of BNP or Pro-BNP as a novel objective prognostic marker in palliative cancer care.

In contrast to the well-established elevation in natriuretic peptides observed in cardiac and renal failure, few studies have examined concentrations of BNP in patients with cancer, or the utility of BNP as a prognostic marker within the last weeks of life. Previous work has demonstrated plasma BNP to be elevated in patients with cancer,[17] and increased BNP concentration to be associated with disease progression,[18,19] reduced progression-free survival,[20] and increased mortality.[18,21–24] Only one small study ($n = 7$) has investigated the role of BNP in patients with advanced cancer, but survival estimates of patients in this study

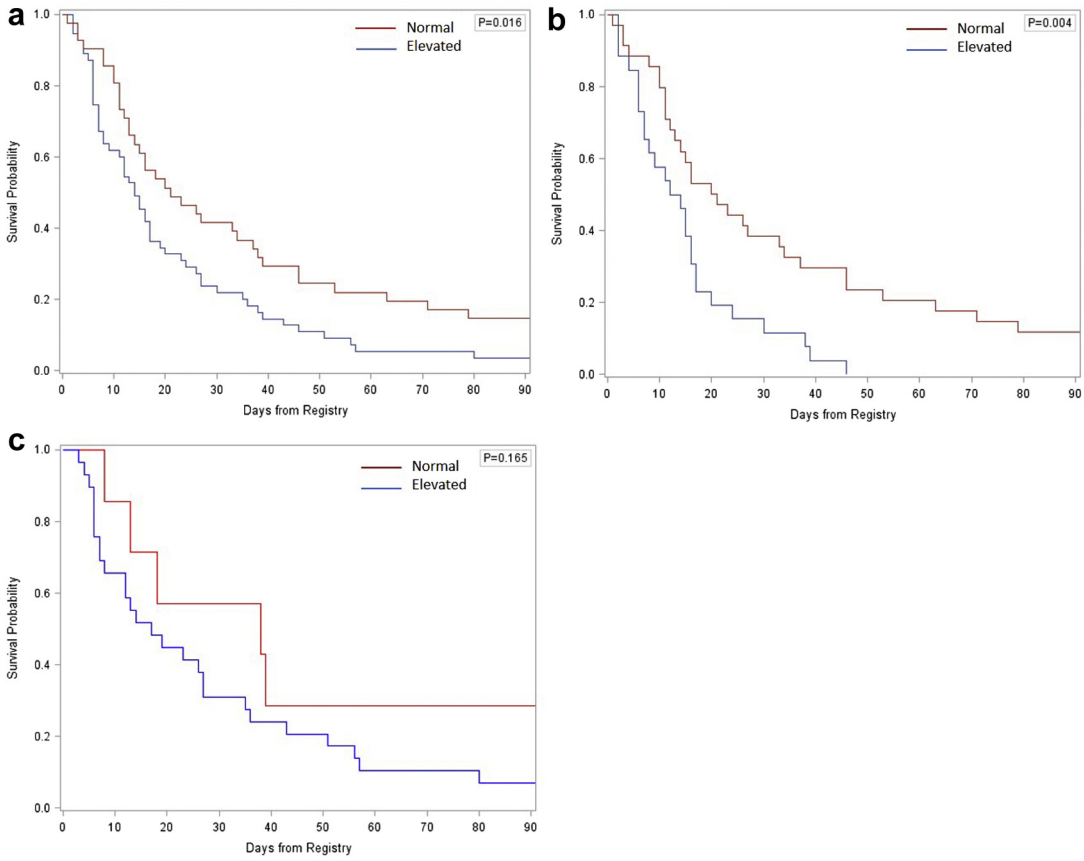

Fig. 1. Association of elevated atrial and brain natriuretic peptides [ANP and BNP; a) ANP, BNP, or Pro-BNP; median (95% CI) survival of 14 (eight to 17) vs. 21 (13–37) days], BNP or Pro-BNP [b) median (95% CI) survival of 13 (seven to 16) vs. 21 (12–34) days], and ANP [c) median (95% CI) survival of 17 (seven to 27) vs. 38 (eight–109) days] with overall survival. Elevations in natriuretic peptide concentrations were defined according to published criteria for acutely decompensated heart failure as >100 and 900 pg/mL for BNP and Pro-BNP, respectively.[15] As no clear diagnostic cutoff has been established for ANP, elevated ANP was defined as per the laboratory upper limit of >77 pg/mL.[16]

were as long as six months.[25] To the authors' knowledge, this study is the first to evaluate the association between plasma natriuretic peptide concentrations and overall survival in cancer patients in the hospice setting. The dearth of data regarding the prognostic utility of BNP, particularly in patients with cancer during the last weeks of life who may be underrepresented in the research setting,[26] highlights the importance of the data presented here.

The elevated concentrations of ANP and BNP observed in the present study cannot be attributed to overt heart or renal failure, because patients with

Table 2
Overall Survival Rate Among Patients With Plasma BNP/Pro-BNP Measured

Plasma BNP or Pro-BNP Concentration	Survival rate (95% CI)						Median Survival (95% CI)
	3 d	7 d	10 d	30 d	60 d	90 d	
Normal	0.97 (0.81–1.00)	0.89 (0.72–0.96)	0.86 (0.69–0.94)	0.38 (0.22–0.54)	0.21 (0.09–0.35)	0.12 (0.04–0.25)	21.0 (12.0–34.0)
Elevated[a]	0.88 (0.68–0.96)	0.73 (0.52–0.86)	0.58 (0.37–0.74)	0.15 (0.05–0.31)	0.00 (0.00–0.16)	0.00 (0.00–0.16)	13.0 (7.0–16.0)
Total	0.95 (0.89–0.97)	0.79 (0.71–0.85)	0.71 (0.62–0.78)	0.34 (0.26–0.42)	0.13 (0.08–0.19)	0.08 (0.04–0.14)	16.0 (13.0–23.0)

BNP = brain natriuretic peptide.
[a]Elevations in natriuretic peptide concentrations were defined according to published criteria for acutely decompensated heart failure as >100 and 900 pg/mL for BNP and Pro-BNP, respectively.[15]

Table 3
Univariate and Multivariate Cox Proportional Hazard Regression Analyses of Elevated BNP or Pro-BNP Association With Overall Survival

	Univariate Analysis		Multivariate Analysis[a]	
Variable	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age[b]	0.997 (0.98, 1.01)	0.61	0.97 (0.95, 0.996)	0.03
Male (vs. female)	0.91 (0.64, 1.30)	0.61	0.40 (0.20, 0.81)	0.01
Race (vs. white)				
Black	0.98 (0.66, 1.48)	0.94		
Hispanic	1.04 (0.61, 1.77)	0.88		
Other	0.97 (0.24, 3.95)	0.96		
Hydration group (vs. control group)	1.02 (0.72, 145)	0.91	0.65 (0.33, 1.27)	0.21
MDAS[b]	1.07 (1.02, 1.13)	0.01	1.05 (0.91, 1.20)	0.52
Elevated BNP or Pro-BNP (vs. normal)[b,c]	2.27 (1.29, 3.97)	0.004	3.09 (1.40, 6.84)	0.005
ECOG[b]	1.55 (1.17, 2.06)	0.002	1.47 (0.68, 3.20)	0.33
Albumin, g/dL[b]	0.57 (0.43, 0.77)	<0.001	0.41 (0.21, 0.81)	0.01
Creatinine, mg/dL[b]	1.16 (0.73, 1.85)	0.53	1.85 (0.89, 3.84)	0.10
Appetite (ESAS score)[b]	1.07 (1.00, 1.14)	0.06	1.12 (0.98, 1.28)	0.09
Dyspnea (ESAS score)[b]	0.99 (0.94, 1.05)	0.68	0.93 (0.82, 1.05)	0.24

BNP = brain natriuretic peptide; HR = hazard ratio; MDAS = Memorial Delirium Assessment Scale; ECOG, Eastern Cooperative Oncology Group performance status; ESAS, Edmonton Symptom Assessment Scale.
[a]Multicovariate model including all variables above except race.
[b]Per unit change, all other variables binary.
[c]Elevations in natriuretic peptide concentrations were defined according to published criteria for acutely decompensated heart failure as >100 and 900 pg/mL for BNP and Pro-BNP, respectively.[15].

clinical evidence of these conditions were excluded from the trial. Subclinical cardiac or renal involvement cannot be excluded, but as all patients were at least mildly dehydrated, the presence of elevated BNP in these patients may point to independent physiological changes occurring within the last weeks of life. Consistent with previous findings, elevated BNP was positively associated with plasma creatinine.[27–31] Elevated BNP was not significantly associated with other prognostic variables, however, again suggesting that BNP may be an indicator of independent physiological end-of-life changes. Previous work has determined elevated BNP to be associated with increasing age,[29,31–33] female sex,[32,33] and European ancestry.[34,35] These associations were observed using very large data sets, so the comparatively small sample size in the present study may have precluded detection in the present study.

Results of the present study have important implications for both research and clinical practice. There are currently few objective prognostic markers in advanced cancer patients in the last weeks of life. Most existing prognostic markers are related to symptoms (delirium, dyspnea, anorexia-cachexia, performance status) and physical signs rather than objective markers, although leukocytosis, lymphopenia, and elevated C-reactive protein are associated with shorter survival.[2,36–38] More recently, phase angle, a marker of cellular integrity, was also identified as an objective prognostic marker in the advanced cancer population.[39] The results presented here provide justification for additional research into physiological changes in the last weeks of life, including examination of the relationship between BNP or Pro-BNP and the aforementioned prognostic factors, as well as investigation of cardiac and renal function as patients approach their final days. On further validation, BNP or Pro-BNP may also provide evaluable prognostic information to augment clinical decision making.[39–43]

This study analyzed data generated from a multicenter randomized controlled trial funded by the National Institutes of Health. The study was also conducted in the unique end-of-life setting among patients with advanced cancer, who may be otherwise underrepresented in research.[26] To the author's knowledge, this study is the first to investigate the prognostic utility of BNP in this unique setting and population, and importantly, still found significant inverse association between plasma BNP concentration and overall survival.

By nature, this post hoc study is hypothesis-generating and exploratory in nature and has several limitations. First, the sample size was small. Second, the stringent inclusion criteria may impede generalizability of study findings. For example, only patients with mild-to-moderate dehydration were included in this clinical trial. Third, ANP, BNP, and Pro-BNP were not consistently collected for all patients. We did not identify any significance between group differences in patient demographics (data not shown). This "random" assignment led us to hypothesize that BNP may be more valuable than ANP as a prognostic marker in patients with advanced cancer at the end-of-life. Fourth, we did not include some known prognostic variables such as C-reactive protein in our

multivariable analysis. Fifth, evaluation of cardiac function was not conducted. Imaging studies to assess cardiac physiology could be highly informative in this population and should be considered in future studies.[44]

This study demonstrated the potential of BNP or Pro-BNP, but not ANP, as a novel objective prognostic marker in patients with advanced cancer during last weeks of life. Additional research is needed to further elucidate the prognostic utility of BNP in this unique population and setting.

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