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ORIGINAL ARTICLE

The prognostic and predictive role of hyponatremia in patients with advanced non-small cell lung cancer (NSCLC) with bone metastases

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Abstract

Purpose Hyponatremia and bone metastasis (BMs) are known as negative prognostic factors in patients affected by metastatic non-small cell lung cancer (NSCLC). Hyponatremia is associated with higher risk of osteoporosis and bone fracture, but no data are available about the relationship between hyponatremia and bone metastasis. This study aims to analyze the prognostic impact of hyponatremia in NSCLC patients with bone metastases.

Methods We retrospectively collected data about advanced NSCLC patients. Survival curves were estimated using Kaplan–Meier method, and comparisons were made using chi-square test.

Results Six hundred forty-seven patients were enrolled into the study. BMs were present in 264 patients (41%) at diagnosis, while hyponatremia appeared in 237 (37%) patients during the first-line treatment. Patients without BMs had a median overall survival (mOS) of 15.9 months (95% CI 14.1–17.9) versus 11.4 months (95% CI 9.4–13.4) for patients with BMs ($p = 0.001$). Eunatremic patients had a better outcome (mOS 16.3 months, 95% CI 14.6–18.0 vs 10.3 months, 95% I 7.6–12.8, $p = 0.003$). Considering the two variables, patients with BMs and hyponatremia had a mOS of 10.1 months (95% CI 4.3–15.9), patients with hyponatremia without BMs 11.9 months (95% CI 11.4–12.4), while mOS was 13.1 months (95% CI 12.0–14.2) for eunatremic patients with BMs versus 17.1 months (95% CI 15.2–19.1) in eunatremic patients without BMs ($p = 0.0020$). Hyponatremic patients developed metachronous BMs significantly earlier (3.73 vs 5.76 months, $p = 0.0187$).

Conclusions Our study showed that hyponatremia is an important prognostic factor and it should be necessarily considered to enhance the management of NSCLC patients with BMs.

Keywords Hyponatremia · Lung cancer · Bone metastasis · Prognosis · Chemotherapy

Introduction

Lung cancer is the leading cause of human cancer deaths worldwide, in both sexes, and its incidence is still increasing [1, 2].

Non-small cell lung cancer (NSCLC) accounts for 85–90% of the totality of lung cancer. Incidence of adenocarcinoma subtype has increased over the last decades as opposed to the squamous histology that decreased [1].

Lung cancer is an aggressive tumor; about 75% of the cases are diagnosed at locally advanced or metastatic stage, mainly involving lymph nodes, the bone, brain, and liver [2].

Despite improvements in the multimodality approach including surgery, radiotherapy, and systemic available treatments, prognosis remains poor. Several factors such as site of disease, stage at diagnosis, and histology may influence prognosis [3].

Lung cancer is the third cause of BMs and skeletal involvement accounts for 350,000 cancer deaths each year [4]. About 30–40% of patients with lung cancer develop BMs during the course of their disease with consequent poor prognosis: the median survival of patients with bone involvement is 7 months [5, 6]. BMs are associated with significant morbidity, loss of functional independence, and reduction in quality of life (QoL)

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[7], resulting in higher social costs due to medical care, hospitalization days, and cost of treatment [8]. BMs due to lung cancer are usually lytic and cause high morbidity through skeletal-related events (SREs), defined as a pathological fracture, surgical intervention, requirement for palliative radiotherapy to bone, spinal cord compression, or hypercalcemia. SREs' occurrence increases the risk of death from 20 to 40% [9].

Another important prognostic and predictive factor for lung cancer patients is hyponatremia, defined as low sodium concentration (< 135 mEq/l). It is the most common electrolyte disorder in lung cancer patients and its estimated incidence varies from 1 to 50% [10–14]. Hyponatremia has a negative correlation with performance status, treatment efficacy, and duration of hospitalization [15–17]. Even mild chronic hyponatremia can lead to marked gait instability and higher incidence of falls [18]. Furthermore, hyponatremia is associated with higher risk of osteoporosis; in fact, reduced extracellular sodium level increases osteoclastic activity that induces impaired bone mineralization [19–21]. However, no data are available about the potential correlation between BMs and hyponatremia.

Given the negative prognostic role of BMs and hyponatremia in NSCLC, our study is aimed to analyze the association between these factors and evaluate the possible worse influence of hyponatremia on prognosis of patients with BMs.

Materials and methods

Study population and data collection

Adult patients with histologically or cytologically confirmed diagnosis of locally advanced or metastatic NSCLC treated with first-line chemotherapy or targeted therapy at three institutions (UniversitàPolitecnica Marche and Campus Biomedico Rome, Italy, and Chelsea & Westminster Hospital, UK) between 1st May 2006 and 31st January 2017 were included into the study. We retrospectively collected data from patients' medical records. Tumor stage was assessed according to the tumor–node–metastasis (TNM) system and included patients with stage IIIB, IV, and IIIA not suitable for surgery, as defined in AJCC version 8 [22].

Treatment with first-line chemotherapy or targeted therapy was continued until evidence of disease progression, unacceptable adverse events, or death. Follow-up generally consisted of regular physical examination and laboratory assessment (hematology and serum biochemistry), and imaging using computed tomography (CT) or magnetic resonance imaging (MRI) according to local procedures every 8–12 weeks.

Overall survival (OS) was defined as the time from beginning of first-line treatment to death, irrespective of cause. Progression-free survival (PFS) was defined as the time from beginning of treatment to progression or to death from any cause, whichever occurred first. Patients without tumor progression or death at the time of the data cutoff for the analysis or at the time of receiving an additional anticancer therapy were censored at their last date of tumor evaluation.

Hyponatremia is defined as serum sodium level < 135 mEq/L and it is considered moderate-severe when < 125 mEq/L.

Statistical analysis

PFS and OS were estimated using Kaplan–Meier method with Rothman's 95% confidence intervals (CI) and compared across the groups using the log-rank test. Patients with a stable disease (SD), partial remission, and a complete remission were considered as responders.

Hyponatremia was assessed within 1 week prior to starting first-line therapy, and before each treatment cycle. Potential factors associated with outcome were evaluated, including patients' age (≥ 65years vs < 65 years), gender, tumor stage, bone metastasis, histology, EGFR mutational status, Eastern Cooperative Oncology Group performance status (ECOG-PS), and smoking history.

Cox proportional hazards models were applied to explore patients' characteristics predictors of survival in univariate and multivariable analyses. Variables not fitting at univariate analysis were excluded from the multivariate model. No-multicollinearity of the grouped covariates was checked. Significance level in the univariate model for inclusion in the multivariate final model was more liberally set at a 0.2 level [23, 24]. The likelihood ratio test was conducted to evaluate the improvement in prediction performance gained by backward elimination of variables from the prognostic model [25].Comparisons were made using chi-square test. All other significance levels were set at a 0.05 value and all p values were two-sided. Statistical analyses were performed using MedCalc version 11.4.4.0 (MedCalc Software, Broekstraat 52, 9030 Mariakerke, Belgium).The research was carried out in accordance with the ethical committee of our institution (ComitatoEticoRegione Marche CERM).All patients gave their written consent to all the diagnostic–therapeutic procedures.

Results

Patient characteristics

Of the 647 patients, treated with first-line therapies at our institutions, 440 (68%) patients were males and 537 (83%) were former or current smokers.

Median age was 72 years (range32–93) and the majority had an ECOG-PS < 2 (556 patients, 86%).Histology was adenocarcinoma in 414 patients (64%), squamous carcinoma in

155 patients (24%), and other histotypes in 78 patients (12%). Tumor stage was III in 158 (24%) patients and IV in 489 patients (76%). Five hundred fifty patients (85%) received a platinum-based first-line chemotherapy while 45 (7%) an epidermal growth factor receptor (EGFR) tyrosine kinase inhibitor (TKI). One hundred five patients (16%) presented with hyponatremia at diagnosis, and a total of 237 (37%) patients developed hyponatremia during the first-line treatment. Twenty-five patients out of these 237 (11%) developed moderate-severe hyponatremia. Five patients (0.8%) presented a diagnosis of syndrome of inappropriate ADH secretion (SIAD). Four (0.6%) patients with SIAD received tolvaptan, 153 (23.6%) patients received saline solution as hyponatremia treatment.

A total of 264 patients (41%) presented BMs (group A), which were synchronous in 170 (26%) patients and metachronous in 94 (15%). Three hundred eighty-three patients (59%) did not develop BMs (group B). No significant differences of clinic-pathological characteristics were shown between the groups, except for a poorer ECOG-PS and a higher presence of concomitant metastasis in group A (Table 1).

Among those, in group A, 92 patients (35%) presented hyponatremia and145 (38%) in group B at diagnosis time.

Overall population

Median OS from diagnosis was 15.9 months (95% CI 12.3 to 16.8) in the overall population. Five hundred and seven patients (78%) died during their follow-up.

Median OS was 14.9 months (95% CI 14.0 to 15.8) and 18.0 months (95% CI 12.6 to 19.2) in non-smokers and smokers respectively ($p = 0.044$). Stratified by gender, median OS was 13.6 months (95% CI 12.5 to 15.1) in males and 16.2 months (95% CI 14.3 to 18.7) in females ($p = 0.003$). Significant difference was found between patients aged < 65years vs ≥ 65years (10.6 vs 13.6 months, $p = 0.003$). Patients with a worse ECOG-PS (≥ 2) had a significantly shorter OS compared to those with ECOG-PS < 2 (10.7 vs 16.5 months, $p = 0.001$).

Based on histology, the median OS was 13.4 months (95% CI 11.7 to 15.1) in patients with non-adenocarcinoma, and 15.7 (95% CI 14.1 to 16.8) in patients with adenocarcinoma ($p = 0.156$). Patients with metastatic disease showed a worse prognosis (12.5 vs 19 months; $p < 0.001$).

According to EGFR status, patients with EGFR wild-type tumors showed a significantly worse OS compared to mutated tumors (25.3 vs 15.8 months, $p = 0.049$).

A significantly worse median OS was described in hyponatremic patients (10.3 months vs 15.3 months; $p < 0.003$) (Fig. 1a). Stratified by BMs presence, patients with BMs had a significantly worse prognosis (median OS of 14.4 vs 15.9; $p = 0.001$) (Fig. 1b).

Table 1 Patients' characteristics

Patients	Overall 647 (%)	BMs 264 (41)	No BMs 383 (59)
Gender			
Male	440 (68)	174 (66)	266 (70)
Female	207 (32)	90 (34)	117 (30)
Age, years	72	65	68
Range	32–93	32–83	34–93
ECOG-PS ≥ 2	91 (14)	55 (21)	36 (9)
ECOG-PS < 2	556 (86)	209 (79)	347 (91)
Histology			
Adenocarcinoma	414 (64)	174 (66)	240 (63)
Squamous carcinoma	155 (24)	58 (22)	97 (25)
Other	78 (12)	32 (12)	46 (12)
EGFR mutation status			
Wild-type	438 (68)	180 (68)	258 (67)
Mutated	54 (8)	39 (15)	15 (4)
Smoking history			
Former/current smoker	537 (83)	216 (82)	321 (85)
Never smokers	110 (17)	48 (18)	62 (15)
Concomitant sites of metastasis			
Lung	440 (68)	174 (66)	266 (70)
Lymph node	278 (43)	140 (53)	138 (36)
Nervous system	155 (24)	71 (27)	84 (22)
Liver	142 (22)	79 (30)	63 (16)
Adrenal gland	104 (16)	63 (24)	41 (11)
First-line therapy			
Platinum-based chemotherapy	550 (85)	232 (88)	318 (82)
Non platinum-based	52 (8)	8 (3)	44 (13)
EGFR-TKI	45 (7)	24 (9)	21 (5)
Hyponatremia			
Yes	237 (37)	92 (35)	145 (38)
No	410 (63)	172 (65)	238 (62)
Response to first-line therapy			
Partial response	188 (29)	61 (23)	127 (33)
Stable disease	227 (35)	100 (38)	127 (33)
Progression disease	232 (36)	103 (39)	129 (34)

At univariate analysis age ≥ 65years, male gender, ECOG-PS ≥ 2, smoking habits, tumor stage IV, non-adenocarcinoma histology, wild-type EGFR status, bone metastasis, and hyponatremia were significantly associated with worse OS (Table 2). At multivariate analysis, male gender, ECOG-PS, tumor stage, bone metastasis, and hyponatremia were independent predictors of a worse OS (Fig 2).

Patients with BMs

Stratifying patients according to the presence BMs and hyponatremia, patients with both factors had a worse prognosis when compared to the remaining patients (10.1 vs

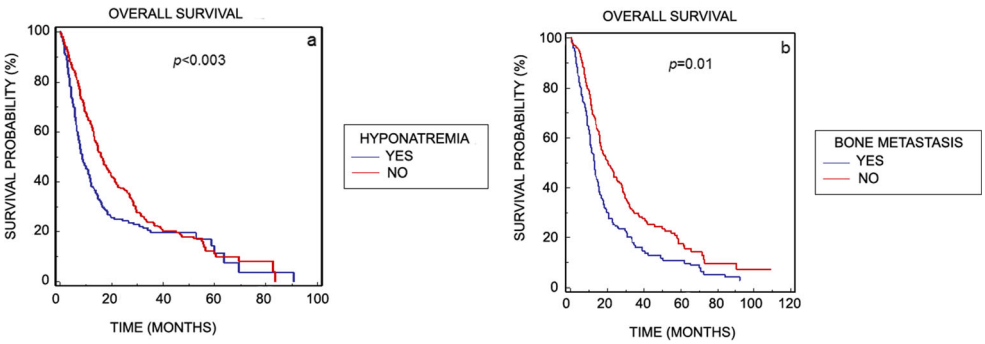

Fig. 1 OS in overall population stratified by serum sodium level (**a**). OS in overall population stratified by presence of BMs (**b**)

15.3 months; $p = 0.0014$). Their outcome was also confirmed poorer when compared to patients with one of the aforementioned features; in fact, mOS was 10.1 (95% CI 4.3–5.9) months for patients with BMs and hyponatremia, 11.9 (95% CI 11.4–12.4) months for patients with hyponatremia without BMs, 13.1 (95% CI 12.0–14.2) months for eunatremic patients with BMs, and 17.1 (95% CI 15.2–19.1) months in eunatremic patients without BMs ($p = 0.0020$) (Fig. 2a).

Considering patients with progressive disease after a first-line treatment and developing BMs, hyponatremic subjects had a significantly shorter PFS (3.7 vs 5.8 months, $p = 0.019$) (Fig. 2b).

Among patients with hyponatremia, median bone progression-free survival was longer in patients that reached hyponatremia correction within 1 month compared to patients with recurrent or unresolved hyponatremia (mPFS 3.03 months vs 2.10 months, HR 0.41 95% CI 0.12–0.67, $p = 0.0040$).

At univariate analysis, age ≥ 65 years and smoking history were significantly associated with worse OS (Table 2); however, these factors were not confirmed at independent prognosticator multivariate Cox regression analysis (Table 3).

Categorical data

BMs were statistically correlated to non-squamous histology ($p = 0.03$). No association between EGFR mutation, TTF-1 expression, and BMs was shown.

Negative TTF-1 expression, squamous histology, and EGFR wild-type status were significantly correlated to a higher risk of hyponatremia ($p < 0.001$; $p = 0.002$; $p = 0.04$ respectively).

Discussion

According to literature, our results showed that BMs occur in 40% of metastatic NSCLC, with an incidence comparable to liver metastasis (25–30%) and contralateral lung metastasis (40–50%) [6, 26–29]. Moreover, in our study, the majority of BMs were synchronous (26%) rather than metachronous (15%). This data was similar to previous studies which showed that 40–80% of BMs were detected at the diagnosis time, and only 30% occurred later, after tumor progression [26–31]. Several studies also suggested that BMs are negative

Table 2 Univariate and multivariable analysis of predictors of OS in patients treated with first-line therapy for locally advanced or metastatic NSCLC. Significant values are reported in italic

Overall survival in the overall population				
	Univariate Cox regression		Multivariable Cox regression	
	HR (95% CI)	*p* value	Exp (b) (95% CI)	*p* value
Age (≥ 65 years vs < 65 years)	1.25 (1.02–1.52)	*0.031*	0.89 (0.84–1.37)	0.596
Gender (M vs F)	1.35 (1.10–1.61)	*0.003*	1.34 (1.01–1.77)	*0.043*
ECOG-PS (≥ 2 vs < 2)	1.91 (1.58–3.61)	*< 0.001* (0.35–1.38)	1.59 (1.03–2.43)	*0.032*
Smoke status (Y vs N)	1.31 (1.01–1.64)	*0.044*	1.35 (0.95–1.89)	0.094
Tumor stage (IV vs III)	1.71 (1.30–1.98)	*< 0.001*	1.51 (1.11–2.09)	*0.011*
Histology (AC vs non-AC)	0.87 (0.72–1.05)	*0.156*	0.89 (0.69–1.15)	0.378
EGFR status (WT vs MT)	1.71 (1.52–1.97)	*0.049*	1.13 (0.45–1.62)	0.665
Hyponatremia (Y vs N)	1.36 (1.12–1.71)	*0.003*	1.29 (1.03–1.54)	*0.047*
Bone metastasis (Y vs N)	1.35 (1.30–1.67)	*0.001*	1.32 (1.03–1.67)	*0.028*

AC, adenocarcinoma; *CI*, confidence interval; *ECOG-PS*, Eastern Cooperative Oncology Group Performance Status; *EGFR*, epidermal growth factor receptor; *F*, female; *HR*, hazard ratio; *M*, male; *MT*, mutated status; *N*, no; *WT*, wild-type status; *Y*, yes

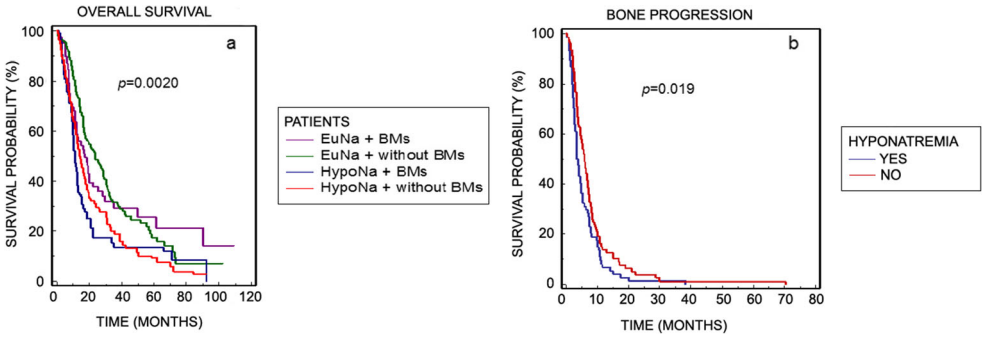

Fig. 2 OS in patients stratifying by the presence of BMs and hyponatremia (**a**). Time to bone progression stratified patients by serum sodium level (**b**)

prognostic factors in NSCLC patients and that in patients with BMs, number of BMs, clinical stage, and serum ALP levels were significantly correlated with prognosis ($p < 0.05$) [32].

Hyponatremia is the most common electrolyte disorder encountered in cancer patients [33]. Hyponatremia has been identified as a negative prognostic factor in different malignancies [34], and it is usually related to prolonged hospitalization, delays in scheduled chemotherapy, worsening of patient PS and quality of life and may also negatively affect treatment response and survival. In particular in lung cancer patients, hyponatremia has been identified as an important negative prognostic factor [35–37].

Hyponatremia is also related with a higher risk of osteoporosis [19–21]. In particular, chronic hyponatremia seems to activate mesenchymal stromal cells, inducing bone loss [38]. Verbalis et al. demonstrated an influence of the mild hyponatremia (serum [Na] 126 to 134 mmol/L) on impaired gait stability and increased risk of falls. In particular, 3 months of mild hyponatremia significantly reduced bone mineral density, decreased bone formation, and increased odds of osteoporosis (*T* score −2.5 or less) at the hip (odds ratio = 2.85; 95%; CI 1.03–7.86; $p < 0.01$) [20].These data suggest that hyponatremia should be considered a prognostic role for osteoporosis and it should be considered in the FRAX score [39]. Pagani et al. demonstrated an influence of the breast metastatic cells on the osteoblastic physiology, in particular on proinflammatory cytokine production, such as IL-8, especially marked by osteoporosis [35]. These studies suggest a role of osteoporosis in the severe hyponatremia and onset of bone metastasis.

However, no data about the association between BMs and hyponatremia in cancer patients are available. Hansen et al. founded an increased proportion of BMs in hyponatremic vs eunatremic patients (17 vs 11%), although without statistical significance [40]. No data are available in NSCLC. Our results did not show an increased incidence of hyponatremia in patients with BMs (35% of patients with BMs presented hyponatremia and 38% in patients without BMs). Jeppesen et al. have demonstrated that hyponatremia (< 136 mmol/L) and presence of BMs were negative prognostic factors in metastatic renal cell carcinomas at univariate and multivariate analyses [41].

Kim et al. in a retrospective analysis of 39 gastric cancer cases with bone marrow dissemination reveal that serum sodium ≤ 133 mmol/L was associated to a poorer outcome ($p < 0.001$) and median survival durations after bone involvement confirmation ($p = 0.013$); [42]. Hyponatremia represents a negative prognostic factor in NSCLC, and its correlation improves patients' outcome [15].

Our results are consistent with those reported by aforementioned studies, showing a worse prognosis in patients with hyponatremia and BMs (OS 11.9 months for hyponatremic patients without BMs, 13.1 months for eunatremic patients

Table 3 Univariate and multivariable analysis of predictors of OS in patients treated with first-line therapy for locally advanced or metastatic NSCLC with bone metastasis. Significant values are reported in italic

Overall survival in population with bone metastasis				
	Univariate Cox regression		Multivariable Cox regression	
	HR (95% CI)	*p* value	Exp (b) (95% CI)	*p* value
Age (≥ 65 years vs < 65 years)	1.40 (0.02–1.90)	*0.036*	1.23 (0.85–1.79)	0.283
Gender (M vs F)	1.20 (0.88–1.71)	0.256		
ECOG-PS(≥ 2 vs < 2)	1.57 (0.99–2.26)	*0.051* (0.35–1.38)	1.53 (0.88–2.70)	0.127
Smoke status (Y vs N)	1.61 (1.08–2.18)	*0.017*	11.1 (0.94–0.02)	0.089
Tumor stage (IV vs III)	1.62 (0.97–2.33)	*0.069*	1.24 (0.89–3.04)	0.112
Hyponatremia (Y vs N)	1.24 (0.91–1.74)	*0.165*	1.15 (0.79–1.67)	0.472

AC, adenocarcinoma; *CI*, confidence interval; *ECOG-PS*, Eastern Cooperative Oncology Group Performance Status; *F*, female; *HR*, hazard ratio; *M*, male; *MT*, mutated status; *WT*, wild-type status

with BMs bone metastasis, 17.1 months for eunatremic patients without BMs). Furthermore, we observed a shorter time to bone progression in hyponatremic patients (3.7 vs 5.8 months, $p = 0.019$).

These results might suggest that, as described by Pagani et al. in breast cancer [35], metastasis cells might induce an inflammatory micro-environment in bones, favoring BMs' onset.

It is therefore important to achieve consensus about the optimal investigation, diagnosis, and management of hyponatremia in order to optimize the outcome of NSCLC patients to prevent BMs' onset.

However, there are limitations to this study. First, it is a retrospective analysis, which is therefore susceptible to bias in data selection and analysis. Secondly, concurrent medication and their influence are the cause and course of hyponatremia cannot be fully accounted.

Nevertheless, for the first time in a large series of NSCLC patients treated with first-line therapy, our results confirm the prognostic value of both BMs and low serum sodium underlying the importance of monitoring hyponatremia in this setting and of a prompt and effective correction of hyponatremia.

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Compliance with ethical standards

Conflict of interest Rossana Berardi and Tom Newsom-Davis have received consulting fee or honoraria from Otsuka.

The other authors declare that they have no conflict of interest.

Ethical approval The research was carried out in accordance with the ethical committee: Comitato Etico Regione Marche CERM.

Informed consent Informed consent was obtained in writing from all individual participants included in the study.

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