The incidence and clinical impact of bone metastases in non-small cell lung cancer

Michael Kuchuk [a], Iryna Kuchuk [a], Elham Sabri [b], Brian Hutton [b], Mark Clemons [a], Paul Wheatley-Price [a,*]

[a] Division of Medical Oncology, The Ottawa Hospital Cancer Centre, Ottawa, & Department of Medicine, University of Ottawa, Ottawa, Canada
[b] Centre for Practice-Changing Research (CPCR), Ottawa Hospital Research Institute, Ottawa, Canada

ABSTRACT

Introduction: Non-small cell lung cancer (NSCLC) is the leading global cause of cancer death. While bone metastases (BM) commonly cause morbidity, bone-targeted agent (BTA) use is variable. We investigated the incidence and impact of BM among unselected NSCLC patients.
Methods: A retrospective chart review of all NSCLC patients seen at a single institution from January 2007 to January 2008 was performed. Various clinical and pathology data were collected. In BM patients, skeletal related events (SRE), interventions and outcomes were recorded.
Results: We identified 383 patients; median age 68 (IQR 60–76); 54% female. Initially 156 patients (41%) were treated with curative intent of whom 91 subsequently relapsed; 227 (59%) were considered palliative from time of diagnosis, including 22 with early stage disease not amenable to radical therapy. Of 296 patients with advanced NSCLC, common metastatic sites were: lung/pleura (80%), mediastinal nodes (69%), bone (39%), brain (30%), and liver (24%). Of 118 patients with BM, 69 (59%) had ≥1 SREs (range 1–18). Common SREs were radiotherapy (63%), pathologic fractures (22%), spinal cord compression (6%) or surgery to bone (5%). Opioid analgesia was required in 69% of BM patients, only 6% of patients with BM received BTA. Overall survival (OS) in pts with mNSCLC was 7.3 months (IQR 3.1–20.5). Pts with BM had significantly shorter OS compared to those without BM (5.8 versus 10.2 months, $p = 0.03$).
Conclusions: BM are common in patients with advanced NSCLC and associated with shorter survival. In this cohort, despite SREs occurred in many patients, BTA were rarely used.

1. Introduction

Despite advances in treatment the overall 5 year survival rate for patients with non-small cell lung cancer (NSCLC) remains around 15%. This is because most patients present with metastatic disease, and many who have initial curative therapy will subsequently relapse [1]. For those patients with advanced disease bone is a common site of recurrence, occurring in 20–40% of patients [1–4]. Once bone metastases (BM) occur, around 80% of patients will experience significant pain [3,5–7] and reduced quality of life [8,9]. In addition over 60% will develop skeletal-related events (SREs) —defined as surgery or radiotherapy to bone; pathological fractures; spinal cord compression or hypercalcemia of malignancy [3,5,10]. Patients who

experience one SRE have a significant risk for developing additional SREs, although it remains unclear as to whether or not the occurrence of SREs affects survival [3,5]. It is evident however that BM has a negative impact on the quality of life and functional status of cancer patients, who may require multiple therapeutic interventions, with an associated impact of increased health care costs [11,12].

Recent studies have shown that osteoclast inhibiting agents such as bisphosphonates, and denosumab, are associated with a reduction in both the risk of, and time to SREs in patient with NSCLC [13,14,15,16,17] and possibly increased survival [18]. However, despite the widespread use of bone-targeted agents (BTA) in patients with bone metastases from breast and prostate cancers [19,20], their use in lung cancer patients has remained much lower [21]. Further, it is not clear whether the clinical trial populations are necessarily representative of an unselected lung cancer population, and as such what the optimal role of BTA in lung cancer should be [22]. In this manuscript we will assess the outcomes for an unselected cohort of NSCLC patients. We will also compare disease outcomes in patients who were initially cured and

* Corresponding author at: Medical Oncology Ottawa Hospital Cancer Centre 501 Smyth Road Ottawa, ON K1H 8L6, Canada. Tel.: +1 613 737 8899x70175; fax: +1 613 1247 3511.

E-mail address: pwheatleyprice@toh.on.ca (P. Wheatley-Price).

subsequently developed BM to those patients who presented with advanced disease but no BM.

2. Methods

2.1. Data collection

With ethics approval, we performed a retrospective chart review of all patients with NSCLC referred to oncology services at our institution in 2007. This included new cases of NSCLC or cases of patients, who were treated with curative intent before 2007, but had relapsed or developed a second lung primary in 2007. The year 2007 was selected in order that patients treated with curative intent were all followed for at least 4 years before data collection occurred. Electronic and paper charts were screened manually to identify eligible patients. All NSCLC patients were included unless there was a history of another malignancy within 5 years.

The data collected included baseline patient demographics data, NSCLC histological subtype, stage at diagnosis, Eastern Cooperative Group (ECOG) performance status (PS) and initial treatment goals (curative versus palliative). For those patients who had been treated with curative intent, their charts were reviewed for evidence of relapse.

For metastatic patients (at diagnosis or relapse) the distribution of their metastatic disease was recorded For those patients with BM the time from lung cancer diagnosis to development of first bone metastases, presentation and distribution of bone metastases, types of SREs, requirements for opioid treatment for bone pain control, and treatment with BTA were recorded. Survival for metastatic patients was measured from the date of diagnosis in patients presenting with advanced disease, or from the date of relapse in patients initially treated with curative intent.

2.2. Statistical methods

Descriptive data are presented as percentages, means ± standard deviations (SD) for normally distributed variables, and medians ± interquartile ranges (IQR) for non-normally distributed variables. To examine differences between any two groups in categorical variables, Chi-Sq Test or Fisher's exact test was used as appropriate. Overall survival was assessed as the primary outcome in this study. Patients who were not followed to death were censored at the time of last follow-up for this analysis. The Kaplan–Meier method was used to estimate the distribution of time to death. To examine differences between any two groups in terms of overall survival, median survival in each group was reported and the Log Rank Test was performed to assess the differences statistically. The Multivariable Cox regression analysis was performed to determine factors associated with longer survival among patients with advanced disease. Pre-specified variables were determined based on clinical experience. Adjusted hazard ratio with 95% confidence interval was reported for each factor.

All statistical tests were 2-sided and considered statistically significant at $\alpha < 0.05$, however we suggest caution in interpretation of p-value bigger than 0.05 as tests are not powered prospectively. The SAS System for Windows version 9.2 (SAS Institute, Inc., Cary, North Carolina) was used for all analyses.

3. Results

3.1. Demographics

Of 439 patients initially identified, 56 were excluded after initial review as they had a second malignancy, or the charts revealed a non-NSCLC diagnosis. Ultimately 383 patients were eligible for

Table 1
Demographic data.

Demographic data	n	%
Gender		
Male	177	46
Female	206	54
Age		
≥70	171	45
<70	212	55
Histologic diagnosis		
Adenocarcinoma	138	36
Sq cell carcinoma	67	17
Large cell carcinoma	22	6
NOS/NSCLC	134	35
Other	22	6
Stage		
1a	35	9
1b	41	11
2a	5	1
2b	27	7
3a	35	9
3b	66	17
4	174	46
ECOG status		
0	86	22
1	128	33
2	72	19
3	68	18
4	29	8

analysis. A study flow chart is shown in Fig. 1 and patient demographics are shown in Table 1. The mean age of the patients was 68 years (range 41–89), 54% were female. Overall 91% were current or ex-smokers. ECOG PS at presentation was 0–1 in 55% of patients, 19% PS 2, and 26% were PS 3-4. The distribution of histological subtypes was adenocarcinoma (36%), squamous cell (17%), large cell (6%) and not otherwise specified (NOS) in 35%. Ten pts (2.6%) had a synchronous pulmonary primary in the second lung.

At initial diagnosis 37% had early stage disease (1–3a), 17% 3b and 46% stage 4 disease.

A total of 156 pts (41%) were treated with curative intent; 227 (59%) were considered palliative at initial diagnosis. Of the 156 curative therapy patients, 91 (58%) subsequently relapsed, with 65 (42%) relapse free when the data for this study was censored. The median time to relapse among patients with curative intent was 23.2 months (95% CI 17.4–33.5). Amongst the 227 patients who were considered palliative at diagnosis, 22 patients had early stage disease (1a–3b) but were not considered candidates for curative therapy. Therefore 205 patients had de novo metastatic disease treated with palliative intent.

3.2. Metastatic disease

In total 296 (77%) patients had metastatic disease (91 relapsed after curative therapy, and 205 with stage 4 at diagnosis). The common sites of metastasis during the course of disease were lung/pleura (83%), mediastinal lymph nodes (71%), bone (40%), brain (31%), and liver (25%) (Table 2). Of note, those diagnosed with de novo stage 4 disease had a significantly higher incidence of bone metastases (48% versus 20%, p < 0.0001) and liver metastases (29% versus 15%, p = 0.01) compared to those who had relapsed after curative therapy.

3.3. Bone metastases at presentation of metastatic disease

Of the 118 patients who developed BM, this occurred at the time of presentation of any metastatic disease in 83 patients, and in 25