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Brain metastases in patients with *EGFR*-mutated or *ALK*-rearranged non-small-cell lung cancers

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Abstract

Introduction—Brain metastases (BM) are common in non-small-cell lung cancer (NSCLC). However, the baseline incidence and evolution of BM over time in oncogene-driven NSCLCs are seldom reported. In this study, we evaluated the frequency of BM in patients with epidermal growth factor receptor (*EGFR*)-mutated or anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC.

Methods—The presence of BM, clinicopathologic data, and tumor genotype were retrospectively compiled and analyzed from a cohort of 381 patients.

Results—We identified 86 *EGFR*-mutated (90.7% with metastatic disease; 85.9% received an EGFR inhibitor) and 23 *ALK*-rearranged (91.3% with metastatic disease; 85.7% received an ALK inhibitor) NSCLCs. BM were present in 24.4% of *EGFR*-mutated and 23.8% of *ALK*-rearranged NSCLCs at the time of diagnosis of advanced disease. This study did not demonstrate a difference in the cumulative incidence of BM over time between the two cohorts (EGFR/ALK cohort

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Conflict of interest: annexed separately.

competing risk regression [CRR] coefficient of 0.78 [95% CI 0.44–1.39], p=0.41). In still living patients with advanced *EGFR*-mutated NSCLC, 34.2% had BM at 1 year, 38.4% at 2 years, 46.7% at 3 years, 48.7% at 4 years, and 52.9% at 5 years. In still living patients with advanced *ALK*-rearranged NSCLC, 23.8% had BM at 1 year, 45.5% at 2 years, and 58.4% at 3 years.

Conclusions—BM are frequent in advanced *EGFR*-mutated or *ALK*-rearranged NSCLCs, with an estimated >45% of patients with CNS involvement by three years of survival with the use of targeted therapies. These data point toward the CNS as an important unmet clinical need in the evolving schema for personalized care in NSCLC.

Keywords

lung cancer; NSCLC; brain metastases; EGFR; ALK; mutation; rearrangement; central nervous system; CNS

INTRODUCTION

Non-small-cell lung cancer (NSCLC) is the leading cause of brain metastases (BM) (1). Amongst those with recurrent/advanced NSCLC, BM are a common culprit for cancer-related morbidity and mortality. The incidence of BM in NSCLC has been reported as >20% at diagnosis, with a significant proportion of patients developing BM over the course of their disease (2, 3). Recent reports also demonstrate an increase in the documented incidence of BM in NSCLC, likely as a consequence of prolonged survival with newer therapies coupled with improvements in neuroimaging modalities (4).

Far less is known about the baseline incidence and subsequent evolution of BM in the subset of patients with oncogene-driven tumors, i.e. epidermal growth factor (*EGFR*)-mutated or anaplastic lymphoma kinase (*ALK*)-rearranged NSCLC (5, 6). Given the growing emphasis on molecular profiling and use of targeted therapeutics (7), this is a critical population. An improved understanding of the incidence and evolution of BM in these cases is therefore an area of ongoing need.

Herein, we report the baseline and cumulative incidence of BM in patients with *EGFR*-mutated or *ALK*-rearranged advanced NSCLC.

MATERIALS AND METHODS

Cohort selection

Patients seen at Beth Israel Deaconess Medical Center (BIDMC) with a diagnosis of NSCLC and whose tumors were genotyped were identified through an ongoing Institutional Review Board-approved study (8,9), with a data cutoff of December 19, 2012 for patient inclusion and June 24, 2014 for outcomes.

Tumor genotype

EGFR mutation analysis (exons 18 to 21) was performed using standard sequencing techniques, and *ALK* rearrangement was analyzed using the Vysis *ALK* break-apart fluorescence in situ hybridization (FISH) probe (8).

Data collection and detection of BM

Data was collected by retrospective chart review and managed using REDCap electronic data capture tools hosted at BIDMC. All patients with advanced NSCLC (stage IV/recurrent disease) had baseline CNS evaluation with either computed tomography (CT) or magnetic resonance imaging (MRI). Subsequent CNS assessment was performed at the discretion of the treating physicians. BM were diagnosed either radiographically or pathologically (tumor resection/biopsy or malignant CSF cytology).

Statistical methods

Fisher's exact test was used to compare categorical variables, and Wilcoxon rank test was used for continuous variables. All p-values reported are two-sided, and tests were conducted at the 0.05-level. Time to BM was defined as the time from diagnosis to date of detected BM, and cumulative incidence curves were fitted and compared using the methodologies of Fine and Gray (10), adjusting for death as a competing risk. Patients not experiencing BM or death by the time of data cutoff were censored at their last date of follow-up. Overall survival (OS) was analyzed using the Kaplan–Meier method. Statistical analyses and curves were performed with the *cmprsk* package in R Statistical Programming Language.

RESULTS

Patient and tumor characteristics

The complete cohort comprised 381 patients, with a median age at diagnosis of 65 years. Self-reported racial groups were 75.9% white, 13.1% Asian, 6.5% black, and 4.4% other. 27.8% of patients were never smokers, 54.9% were former smokers, and 17.3% current smokers. At the time of initial entry into the cohort, 73.8% had stage IV/recurrent disease, and 86.1% had adenocarcinoma histology. *EGFR* and *ALK* analysis was successful in 94.2% (359/381) and 91.6% (252/275) of tested samples, respectively (8). The overall frequency of *EGFR* mutations and *ALK* FISH positivity was 23.9% (86/359) and 9.1% (23/252), respectively. Abnormalities in *EGFR* and *ALK* were mutually exclusive in all genotyped tumors.

Characteristics of *EGFR*-mutated or *ALK*-rearranged NSCLCs

The *EGFR*-mutated cohort was comprised of more women; however, both cohorts predominantly involved patients with no tobacco history, advanced disease, and adenocarcinoma histology (Table 1). 85.9% (67/86) of patients with *EGFR*-mutated NSCLCs received an EGFR tyrosine kinase inhibitor (TKI) -gefitinib, erlotinib, or dacomitinib – at some point in their treatment course. 85.7% (18/23) of patients with *ALK*-rearranged NSCLCs received the *ALK* TKI, crizotinib (Table 1). The median follow-up for patients with *EGFR*-mutated and *ALK*-rearranged NSCLC was 45.2 and 36.4 months, respectively.

BM in *EGFR*-mutated NSCLC

24.4% (19/78) of the patients with *EGFR*-mutated NSCLC had BM at initial evaluation. The cumulative incidence of post-diagnosis BM increased over time (Figure 1A): 34.2% at 1 year, 38.4% at 2 years, 46.7% at 3 years, 48.7% at 4 years, and 52.9% at 5 years.

BM in *ALK*-rearranged NSCLC

23.8% (5/21) of the patients with *ALK*-rearranged NSCLC had BM at initial evaluation. The cumulative incidence of post-diagnosis BM increased over time (Figure 1A): 23.8% at 1 year, 45.5% at 2 years, and 58.4% at 3 years. At the time of data cutoff, none of the patients with *ALK*-rearranged NSCLC had reached beyond the 4-year survival mark.

Differences in BM between *EGFR*-mutated and *ALK*-rearranged NSCLC

No statistically significant difference was observed in the baseline and subsequent incidence of BM with *EGFR*-mutated versus *ALK*-rearranged tumors (Figure 1A). Additionally, this study did not demonstrate a difference in the cumulative incidence of BM over time between the two cohorts (*EGFR/ALK* cohort CRR coefficient of 0.78 [95% CI 0.44–1.39], p=0.41). However, since the *ALK*-rearranged cohort had fewer patients and less follow-up time than the *EGFR*-mutated group, it is unknown if differences may have evolved during subsequent follow-up.

Overall survival

Survival curves are depicted in Figure 1B. Amongst the 78 patients with an *EGFR* mutation, the median OS was 34.4 months (95% CI 28.1–49.1). Median OS amongst the 21 patients with an *ALK* rearrangement was 38.3 months (95% CI 22.3-NA).

DISCUSSION

We retrospectively evaluated a cohort of patients with *EGFR*-mutated or *ALK*-rearranged advanced NSCLC. BM were common, with nearly 25% of patients with BM at initial diagnosis and approximately half of patients with BM by 3 years in the setting of precision therapies. Limitations of this study include its retrospective nature and the lack of a standardized protocol for CNS assessment. Nevertheless, to our knowledge, this is the largest study to assess the baseline incidence and subsequent evolution of BM in these molecularly-defined groups.

The clinical course of patients with these oncogene-driven NSCLCs is an area of ongoing investigation. The University of Colorado evaluated patterns of metastatic spread in 209 patients with treatment-naïve *EGFR*-mutated, *KRAS*-mutated, *ALK*-rearranged, and *EGFR/KRAS/ALK*-unaffected advanced NSCLC (11). Similar to our findings, BM was present at diagnosis in 23% and 24% of *EGFR*-mutated and *ALK*-rearranged patients, respectively (11). In one retrospective study, BM were reported in 8% (5 of 62) *EGFR*-mutated patients at diagnosis, with an additional 24% diagnosed with BM at follow-up (12). The overall incidence of BM in this cohort was 32%, and time to BM and post-BM survival were 20.8 and 12.1 months, respectively (12). One other study of 93 patients with NSCLC and BM undergoing mutational analysis for *EGFR* found 49% (20 of 41) of *EGFR*-mutated NSCLCs

with synchronous BM at the time of initial diagnosis (13). Time to progression in the brain was non-significantly longer in *EGFR*-mutated NSCLCs as compared to those with wild-type *EGFR* (13). The prevalence of BM in the published trials of TKIs in advanced NSCLC to-date is similarly impressive, with more than 10% of patients in the first line trials of EGFR TKIs (5) and 35% of patients in the second line trials of ALK TKIs (6) noted to have baseline asymptomatic BM.

As targeted therapies continue to improve outcomes for patients with molecularly-driven NSCLCs (5–7), the deterrence of BM has become an increasingly relevant therapeutic dilemma. Most available TKIs (gefitinib, erlotinib, and crizotinib) inefficiently cross the intact blood–brain barrier with cerebrospinal fluid-to-plasma ratios as low as 0.01 to 0.003 detected in patients (14). Even so, it seems that their use can still alter the natural history of BM. In one report of 155 *EGFR*-mutated NSCLCs, the 12- and 24-month cumulative risk of CNS progression was 6% and 21% in the group initially treated with an *EGFR* TKI, as compared to 19% and 32% in the group receiving first line chemotherapy; a hazard ratio of 0.56 (95% CI 0.34–0.94) was noted for CNS progression, favoring upfront *EGFR* TKI over chemotherapy (15). Although a similar comparison has not been performed for *ALK*-rearranged NSCLC, crizotinib and other *ALK* TKIs (such as ceritinib and alectinib) can also positively influence CNS disease (7). Ceritinib and alectinib have reported CNS activity in patients with ALK-rearranged NSCLC that are naïve or resistant to crizotinib therapy (7). Since our group's cohort and those of others (5–7) predominantly studied patients that received TKIs, it is tempting to postulate that the cumulative incidence of BM may have been even higher in patients treated with chemotherapy alone. Contemporary clinical trials of novel EGFR and ALK TKIs now mandate baseline CNS imaging at study entry for all patients and have started to stratify patients based on presence/absence of BM. Such efforts will hopefully define prospectively whether CNS and systemic sites differ in patterns of response/progression in the setting of TKI use (7). Moreover, these studies will aid in delineating strategies for optimal surveillance for and detection of BM early in the course of CNS progression, for which there is currently no established standard.

Acquired resistance to targeted therapies remains a key limitation in achieving a durable benefit. Even as the major mechanisms of acquired systemic resistance are known to result from resistant tyrosine kinase mutations and activation of bypass pathways (7), the mechanisms that explain CNS progression remain largely unknown. As reported here and elsewhere (5–7, 10–12), the CNS is amongst the most frequent sites of disease progression in patients whose systemic disease is otherwise being successfully controlled with TKIs. The optimal management of BM in oncogene-driven NSCLCs remains uncertain, and the use of whole brain or stereotactic radiotherapy remains a cornerstone of care (16).

In conclusion, this retrospective study demonstrates the high initial incidence (nearly 25%) and subsequent prevalence of BM in patients with advanced *EGFR*-mutated or *ALK*-rearranged NSCLCs treated with TKIs. Given their frequency in tumors with these driver mutations, increased inclusion of patients with BM in innovative trials of targeted therapies will be critical in defining their full potential and facilitating their application in real-world practice. Developing optimal strategies for the prevention and management of CNS disease has become one of the foremost clinical questions in the care of these patients. Future

studies should address the role of TKIs with improved CNS penetration, the use of less toxic radiotherapy techniques for BM, and the need to better understand the molecular underpinnings of malignant CNS disease.

Acknowledgments

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HIGHLIGHTS

- Brain metastases are frequent in *ALK* rearranged lung cancers

- Brain metastases are frequent in *EGFR* mutated lung cancers

- ~25% of patients at diagnosis and half at 3-years of survival have brain metastases
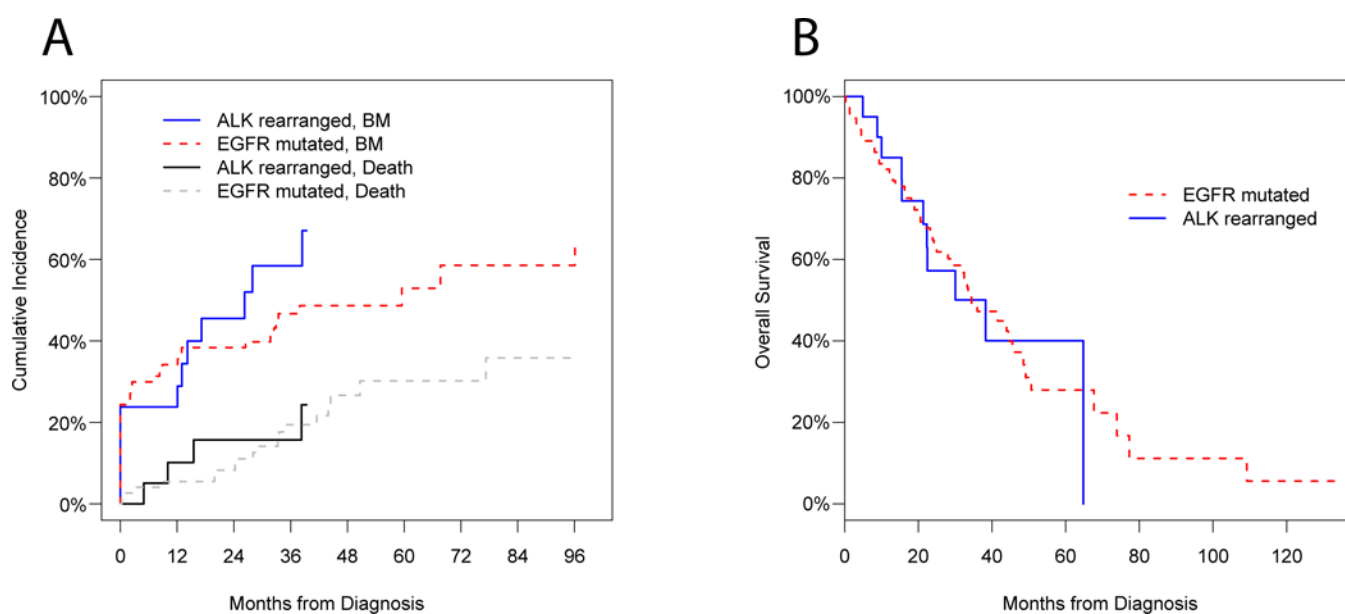
Figure 1.

Table 1

Baseline characteristics of patients and tumors with *EGFR*-mutated and *ALK*-rearranged NSCLC.

	Tumor genotype		
	EGFR-mutated (n=86)	*ALK*-rearranged (n=23)	*p*-value
Age at time of biopsy			
Median (range)	65 (33–90)	56 (29–80)	<0.0001[*]
Women n (%)	64 (74.4)	11 (47.8)	0.0218
Race n (%)			
White	50 (58.1)	15 (65.2)	0.6357
Asian	31 (36.1)	4 (17.4)	
Black	4 (4.6)	0 (0)	
Other	1 (1.2)	4 (17.4)	
Smoking status n (%)			
Current smoker	4 (4.65)	1 (4.3)	0.4909
Former smoker	37 (43.0)	8 (34.8)	
Never smoker	45 (52.3)	14 (60.9)	
Stage n (%)			
I–III	8 (9.3)	2 (8.7)	1.0000
IV/recurrent	78 (90.7)	21 (91.3)	
Histology n (%)			
Adenocarcinoma	84 (97.7)	21 (91.3)	0.1952
Squamous cell carcinoma	0 (0)	1 (4.3)	
NSCLC (NOS)	2 (2.3)	1 (4.3)	
Use of precision TKI n (%)			
When stage IV/recurrent	67 (85.9)	18 (85.7)	1.0000
Baseline brain metastases n (%)			
When stage IV/recurrent	19 (24.4)	5 (23.8)	1.0000

NSCLC = non-small-cell lung cancer; NOS = not otherwise specified; TKI = tyrosine kinase inhibitor.

[*] Wilcoxon-Rank Sum test