Brain Metastasis and Epidermal Growth Factor Receptor Mutations in Croatian Caucasians with Lung Adenocarcinoma

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treatment seemed to improve outcome. Whilst lacking QOL data and a supportive care control group, our data would suggest that for selected patients, especially those of good PS there remains a role for WBRT in NSCLC.

Keywords: NSCLC, Brain metastasis, WBRT, non-small cell lung cancer

P2.03b-008
The Impact of Brain Metastases and Their Treatment on Health Utility Scores in Molecular Subsets of Lung Cancer Patients

Topic: Brain Meta

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Background: New therapies, particularly in advanced patients with EGFR-mutated and ALK-rearranged tumors, result in prolonged survival. Brain metastases and/or their treatment, may have a negative impact on health-related quality of life. Technological assessment of the cost-effectiveness of various treatments for brain metastases will benefit from measurements of health-related qualify of life and health utility scores (HUS). This study evaluated the impact of brain metastases on HUS across multiple health states defined on the basis on disease stability, brain-specific therapies, and molecularly-defined subsets of NSCLC.

Methods: A longitudinal cohort study at Princess Margaret Cancer Centre evaluated 1571 EQ5D-3L-derived HUS in 476 Stage IV lung cancer outpatients, from Dec, 2014 through May, 2016: *EGFR+* (n=183), *ALK+* (n=38), wild-type (WT) non-squamous (n=171), squamous (n=29), and small cell lung cancer (SCLC) (n=30). Patients were stratified according to presence or absence of brain metastases at the time of assessment; mean HUS (± standard error of the mean, SEM) by presence of brain metastases and various health states and disease subtypes were reported. For patients with repeated measures, only the earliest time point was analyzed.

Results: 172 patients had brain metastases, median age 62 (range 32-86) years and 304 patients did not have brain metastases, median age 66 (29-96) years. Overall HUS was related to disease subtype but not presence of brain metastases: *EGFR/ALK+* patients with (0.78±0.02) or without brain metastases (0.79±0.01) *versus* WT/SCC/SCLC with (0.74±0.02) and without brain metastases (0.73±0.01) ($p=0.01$ by subtype; $p>0.10$ by presence of brain metastases). However, symptomatic CNS disease (0.69±0.04) had lower HUS (*versus* asymptomatic disease (0.77±0.02)) ($p=0.03$). Patients achieving intracranial stability or response to treatment had significantly higher HUS (0.81±0.05) than patients with progressive CNS metastases (0.72±0.02) ($p=0.03$). Extra-cranial control also correlated with higher HUS (0.81±0.02 *versus* 0.69±0.03, $p<0.0001$). When local treatment for brain metastases was delivered within 6 months, HUS was lower (0.71±0.02 *versus* 0.82±0.02, $p=0.0005$). CNS disease treated only with systemic therapy or on no active therapy had mean HUS of 0.81±0.03, while patients treated only with stereotactic radiosurgery (SRS) had values of 0.80±0.04; there was a trend for lower HUS with whole brain radiation (WBRT) only (0.72±0.03) or WBRT+SRS (0.74±0.03) ($p=0.11$).

Conclusion: Brain metastasis stability has significant impact on HUS in lung cancer patients. Treatment modalities of brain metastases may also impact HUS. Data collection is ongoing; updated HUS data including longitudinal assessments and multivariable analyses will be presented.

Keywords: brain metastases, health utility scores, NSCLC

P2.03b-009
Brain Metastasis and Epidermal Growth Factor Receptor Mutations in Croatian Caucasians with Lung Adenocarcinoma

Topic: Brain Meta

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Background: The brain is a common site of metastasis in non-small cell lung cancer (NSCLC). The aim of this study was two-fold: 1) to determine the incidence of brain metastasis (BM) in Caucasian lung adenocarcinoma patients with epidermal growth factor receptor (EGFR) mutations and 2) to evaluate the frequencies and potential relationship of the different EGFR mutations with BM.

Methods: A retrospective cohort study was conducted at a Croatian tertiary hospital (Clinic for Respiratory Diseases "Jordanovac") using data collected from medical records. Caucasian patients with primary NSCLC who were tested for EGFR mutation status between January 2014 and October 2015 were included.

Results: Of 1040 NSCLC samples tested, 122 (11.7%) patients with lung adenocarcinoma harbored EGFR mutations; six EGFR positive (+) patients (four with BM) had repeat EGFR testing. The majority of EGFR mutants were females (n= 90, 77.6%), non-smokers (including never-smokers and former-smokers; n= 95, 92.2%), diagnosed with advanced disease (stage IIIB/IV) at first presentation (n= 75, 68.8%), and median age at initial diagnosis of primary lung cancer was 65 years (35 - 90). Twenty-three (19.8%) of 116 EGFR+ patients were diagnosed with BM; for six EGFR+ patients, data about BM was missing. Most were 64 years of age or younger (n= 15, 65.2%) at diagnosis of BM (median age: 62 years, 48 - 72). Synchronous BM disease at initial diagnosis of lung cancer was found in 43.5% of EGFR+ patients with BM (n= 10). There were more EGFR+ women with BM (n= 20, 87%) than men. Single exon 19 deletion and exon 21 L858R mutations were the most common subtypes in both EGFR+ patients without BM (n= 44, 47.3% and n= 27, 27.8%, respectively) and with BM (n= 13, 56.5% and n= 5, 21.7%, respectively). One BM patient (4.3%) had a double mutation (exon 19 and 21), while six non-BM patients (6.2%) had simultaneous pairings, most commonly between exon 19 and 20 (n=3, 3.1%). Although exon 18 mutations were seen in six patients without BM (6.2%), none were found in BM+EGFR+ patients. Exon 20 T790M mutation occurred in 17.4% of BM patients (n= 4) versus 15.3% of non-BM patients (n= 15). Rare EGFR double mutations (exon 18 and 20) were found in two non-BM patients (2.2%).

Conclusion: Larger long-term prospective studies to explore and confirm these results in BM+EGFR+ patients are warranted. In the era of precision oncology, molecular testing of EGFR mutations may further clarify the pathogenesis of lung cancer-associated BM.

Keywords: precision medicine, brain metastases, non-small cell lung cancer, Epidermal growth factor receptor mutations

P2.03b-010
EGFR Mutation Status Analysis in Cerebrospinal Fluid and Plasma of Advanced Lung Adenocarcinoma with Brain Metastases

Topic: Brain Meta

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Background: We aimed to investigate the feasibility of droplet digital PCR (ddPCR) for the detection of epidermal growth factor receptor (EGFR) mutations in circulating free DNA (cfDNA) from cerebrospinal fluid (CSF) and plasma of advanced Lung Adenocarcinoma (ADC) with brain metastases (BM).

Methods: Fourteen advanced ADC patients with BM carrying activating EGFR mutations in tumor tissues were enrolled in this study, and their matched CSF and plasma samples were collected. EGFR mutations were detected by the Amplification Refractory Mutation System (ARMS) in tumor tissues. EGFR mutations, including 19del, L858R, and T790M were examined in cfDNA isolated from 2 milliliter CSF or plasma by ddPCR assay. The clinical response was assessed according to Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1 guidelines. Overall survival (OS) and progression free survival (PFS) after the diagnosis of BM were also evaluated.

Results: Out of 14 patients, eleven were females and three males aged from 34 to 74 years old (median age of 55 years old). In all of cases, CSF cytology were negative. In ddPCR assays, EGFR mutations were detected in CSF of three patients (21.4%; one of 19del and two of L858R), and in plasma of six patients (42.9%; one of 19del, one of L858R, one of T790M, two of L858R&T790M, and one of 19del&T790M). All EGFR T790M mutations were found during or after EGFR-TKIs treatments. The three patients with activating EGFR mutations in CSF achieved partial response (PR) of BM after treated with combination of WBRT and EGFR-TKIs. The median OS and PFS after the diagnosis of BM were 18.0 months and 9.0 months, respectively.