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Case Report

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Dabrafenib resistance overridden by switch to vemurafenib and trametinib in 53-year old patient with metastatic lung carcinoma: clinical case report

Abstract

Introduction: A small subset of patients with Adeno-carcinoma of the lung harbor mutations in BRAF, a proto-oncogene involved in cell signaling. Acquired resistance to BRAF inhibition has been reported in nearly half of patients with metastatic melanoma who are treated with BRAF inhibitors. Resistance to BRAF inhibition has been ameliorated by co-targeting additional sites in the RAS/RAF/MEK pathway.

Methods: Oral Trametinib (2mg, once, daily) and oral Vemurafenib (960mg, twice, daily) were administered as combination therapy for treatment of BRAF V600E mutated non-small cell lung cancer which had become refractory to Dabrafenib after prolonged initial response.

Case Report: We report the case of a 54 year old male who presented with stage 4 Adenocarcinoma of the lung with pleural effusion and metastases to the brain, liver and bone. Molecular profiling confirmed a mutation in BRAF V600E and the patient was subsequently treated with the BRAF inhibitor Dabrafenib, which he initially responded to. Significant disease progression was indicated by PET/CT and MRI and it was determined that the patient had become resistant to Dabrafenib. The patient's resistance was overridden by co-targeting BRAF and MEK with Vemurafenib and Trametinib.

Conclusion: This case highlights the potential efficacy of targeted therapy in patients with Adenocarcinoma of the lung with BRAF mutations. While patients may initially respond to inhibition of a single target, the high probability of developing resistance suggests the importance of examining effective combination of alternative BRAF inhibitors combined with MEK inhibition for malignancies other than melanoma.

Keywords: adenocarcinoma, BRAF, MEK, targeted therapy, acquired resistance

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Introduction

Mortality from lung cancer is greater than the combined mortality of the next three most common forms of cancer (breast, colon, and pancreatic).[1] Adenocarcinoma of the lung is an aggressive disease with the potential to metastasize to any organ system in the body. BRAF is a proto-oncogene associated with a number of cancers, which encodes the B-Raf protein, a signaling molecule involved in directing cell growth. Mutations in BRAF are found in up to 4% of patients with non-small cell lung cancers, the majority of which are Adenocarcinoma.[2] Targeted therapy involving BRAF inhibition is a potential approach to the treatment of the small subset of NSCLCs in which a BRAF mutation is involved. However, resistance to BRAF inhibitors poses a significant challenge to achieving long-term remission. We report the case of a 54 year old nonsmoker with metastatic Adenocarcinoma with a BRAF mutation. The patient was effectively treated with the BRAF inhibitor Dabrafenib but acquired a subsequent resistance, which was successfully overridden by a change to Vemurafenib coupled with the MEK inhibitor Trametinib. Pharmacological treatments were supplemented by administration of IV Vitamin C, Glutathione, Taurine, and Lysine. The clinical, radiological and molecular features of this case are discussed.

Methods

The patient was administered targeted combination therapy for the treatment of metastatic Adenocarcinoma of the lung. Oral Trametinib (2mg) was given once daily and oral Vemurafenib (960mg) was given twice daily. Imaging studies, including MRI of the brain with and without contrast and PET/CT of the body and extremities, were performed regularly (every 3 months) to assess changes.

Case presentation

A 54-year-old male with a history of stage 4 Adenocarcinoma with pleural effusion and metastasis to the brain, liver and bone presented to the clinic on November 2012 because of disease progression. Upon examination, the patient complained of weight loss, fatigue and appetite loss. The patient's relevant medical history began in April 2008, when a routine dermatology follow up for cutaneous melanoma demonstrated a palpable left supraclavicular lymph node, which was subsequently determined to be a poorly differentiated Adenocarcinoma with papillary features. A chest CT revealed several lymph node tumors as well as a primary tumor in the right lung. The patient began a course of Alimta and Avastin in June 2008. Both were well tolerated and the patient showed a good response to these treatments. A series of additional CT scans performed in June and July of 2008 demonstrated possible bone metastases at which point Carboplatin and IV Zolendronic Acid were added to his treatment.

Imaging studies done in November and December of 2008 as well as February of 2009 demonstrated significant improvement and possible remission. The patient continued to show signs of remission and was generally asymptomatic throughout 2009. PET/CT performed in January 2010 demonstrated some changes however because of a possible upper respiratory infection the patient was

treated with Avalox and advised to do a follow up scan in two weeks' time. The patient showed no signs of disease progression and was asymptomatic; however follow up studies done in April 2010 showed additional unfavorable changes. In June 2010, due to the results of recent scans as well as a bronchoscopy he was restarted on Alimta, Avastin, and Carboplatin.

A follow up CT in the fall of 2010 showed evidence of a pleural effusion, which were drained in the following spring prior to a second bronchoscopy. The obtained fluid was found to contain tumor cells and molecular profiling performed on tissues collected from the bronchoscopy indicated a BRAF V600E mutant non-small cell Adenocarcinoma. Subsequent to this finding, in June 2011 the patient was approved for a GSK BRAF inhibitor trial protocol at John Hopkins Hospital. At this time, an MRI of the brain demonstrated evidence of small brain metastases, which were successfully treated with stereotactic radio surgery (RadRx). The patient began treatment with the BRAF inhibitor, Dabrafenib in August 2011. Despite a good response to Dabrafenib, pleural effusion persisted with little improvement and a Pleur X catheter was inserted in November 2011. In 2012 the patient complained of various upper respiratory symptoms including nasal congestion, postnasal drip, and a severe associated cough. These symptoms progressed over several months until they were found to be intolerable, at which point the patient opted to discontinue use of Dabrafenib. After discontinuation, the upper respiratory symptoms began to abate. While brain MRI and chest CT indicated favorable response to BRAF inhibition, novel lesions were found in the patient's liver which were subsequently treated with radio surgery.

After experiencing worsening symptoms in November 2012, the patient presented to our integrative clinic to discuss treatment options for slowing the progression of his disease. Thoracic and Abdominal/ Pelvis CT performed in December 2012 demonstrated increased nodular thickening at the base of the right hemi thorax and multiple scattered hypo attenuating lesions throughout the liver, both consistent with worsening metastatic burden. At this time, the patient was administered Abraxane and Zaltrap as well as Leukine, Proleukine and Glutathione. An April 2013 PET/CT of the body and extremities indicated overall improvement in osseous metastases (Figure 1), however a large amount of pleural effusion was noted near the right apex, which had progressed from the previous study. At this time the patient discontinued Abraxane, but continued Zaltrap and began courses of Zometa, Temodar, and Stivarga. Continued improvement was observed throughout April and into May at which time symptoms of hand and foot syndrome became apparent. As a result, the patient discontinued use of Stivarga. Symptoms of hand and foot syndrome subsequently abated.

A PET/CT of the body and extremities performed in July 2013 showed evidence of disease progression with a new metabolically active lymph node noted within the porta hepatis along with new metabolic activity in the right axilla and increased metabolic activity in multiple osseous metastases. An MRI of the brain performed in July indicated the development of innumerable enhancing metastatic lesions throughout the supratentorial and infratentorial brain with associated vasogenic edema. At this time, the patient was restarted on Abraxane and because of his history of a good initial response to Dabrafenib, was administered the BRAF inhibitor Zelboraf. Zelboraf administration was maintained and the dosage was increased over the course of 6 weeks. Despite complaints of poor appetite and some recurring seizures, the Zelboraf was well tolerated and the patient's disease was stable.

In February 2014, the MEK inhibitor Trametinib and Gemzar were added to the patient's treatment regimen. Both were well tolerated and the patient reported improvements in symptoms, noting decreases in fatigue and weight loss as well as an improvement in appetite. An MRI of the brain performed in March 2014 demonstrated significant interval reduction in size and number of metastatic foci and associated vasogenic edema previously identified throughout the cerebrum and cerebellum in previous scans (Figure 2). Subsequent scans indicated that these improvements were maintained. A PET/CT of the body and extremities performed in May 2014 showed interval improvement of previously identified sclerotic multifocal osseous metastatic disease with no observed metabolic uptake (Figure 3). Furthermore, the previously observed hyper metabolic medial upper lobe pleuroparenchymal opacity was no longer present. In addition to these improvements, throughout April, May and June, marked improvements were reported in the patient's appetite, weight, fatigue and general well-being. A steady decline in the patients CEA levels was also observed throughout this period. At the time of this writing, the patient remained on Zelboraf and Tremetinib, both of which continued to be well tolerated.

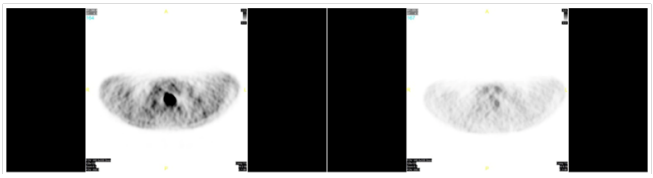

Figure 1 PET/CT of Body and Extremities demonstrating improvement in osseous metastases. Right image (January 2013) shows hypermetabolic metastatic lesion at t2 with SUV of 8.7g/ml. Left image (April 2013) shows lesion as signifigantly less hypermetabolic with SUV of 2.9g/ml.

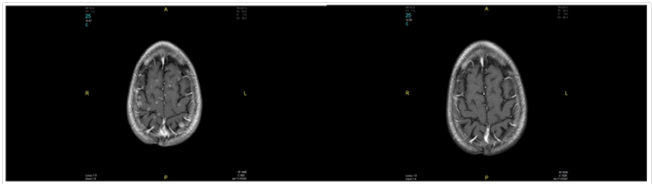

Figure 2 MRI of the brain showing markedly diminished number and size of multiple enhancing metastatic foci. The left image (July 2013), shows innumerable enhancing metastatic lesions throughout the supratentorial and infratentorial brain. The right image (March of 2014) shows a significant interval reduction in size and number of metastatic foci.

Figure 3 PET/CT of body and extremities showing improvement in hypermetabolic activity in bones of right hemipelvis. Left image (March 2014) shows abnormal activity in right iliac bone with SUV of 3.4g/ml. Right image (May 2014) shows same area 2 months later with less uptake and SUV of 2.9g/ml.

Discussion

Adenocarcinomas are epithelial neoplasms of glandular origin, glandular characteristics, or both. Nearly 40% of lung cancers are Adenocarcinoma with these being the most common type of tumor among non-smokers.[3,4] In contrast with small cell lung cancer and squamous cell lung cancer, which are generally observed to be medially located, Adenocarcinoma is typically found in the peripheral

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regions of the lungs.[5,6] As with all cancers, early diagnosis of lung Adenocarcinoma is associated with better outcomes and lower risk of metastatic disease.

Staging of non-small cell lung cancer is based on tumor size and location, regional lymph node involvement and extent and distance of metastases. The most commonly used staging methodology is the American Joint Commission on Cancer (AJCC) TNM system. In stages I and II, tumors are ≤ 7cm across and only found in lung tissues and lymph nodes on the same side as the primary tumor. In stages IIIA and IIIB the main tumor can be of any size. If cancer has only grown into lymph nodes and lung tissue on the same side as the original tumor it is called IIIA. If tumors have invaded lymph nodes on the side opposite the primary tumor or have grown into the large vessels of the heart, trachea, esophagus, or proximal spine it is considered IIIB. Adenocarcinomas are categorized as Stage IV when tumors have spread to the opposite lung, when a malignant plural effusion or pericardial effusion is identified and/or if metastases are detected in additional organs including the brain, liver, or bones. The 5-year survival rate for patients with localized disease (Stages I and II) is between 31-49% depending on the size of the primary tumor and extent of regional growth. However, once the tumor has spread to distant sites, this rate drops sharply to approximately 1%.[7] As such, better outcomes rely on early detection and diagnosis.

BRAF is a proto-oncogene which encodes the intracellular Kinase, B-Raf. B-Raf acts as catalyst for the phosphorylation of serine and threonine residues on target proteins in the RAS/RAF/MEK/ERK/ MAP Kinase signaling pathway which directs cell growth, survival, differentiation, and secretion. Mutations in BRAF result in tumor growth by causing constitutive signaling in this pathway and subsequent deregulation of the processes it sub serves.[8,9] While most notably associated with malignant melanoma, acquired mutations in BRAF have also been found in non-hodgkins lymphoma, colorectal cancer, and Adenocarcinoma of the lung.[10] A series of studies have identified BRAF mutations in patients with various forms of NSCLC. In a DNA sequencing study of 883 patients with NSCLC performed by Cardarella et al.[2] 36 (4%) patients were found to harbor BRAF mutations. Of these 36, 18 were found to be V600E and the remaining were assorted non V600E mutations. Paik et al.,[11] found BRAF mutations including V600E, G469A and D594G, in 3% of 697 patients with Adenocarcinoma of the lung. From the analysis of BRAF sequences in primary human lung Adenocarcinoma, Naoki et al.,[12] identified G465V and L596R mutations in exons 11 and 15 in 2 of 127 tumor specimens (1.6%). These findings as well as those from additional investigations, suggest the importance of examining BRAF as a viable target for anticancer medications in NSCLCs.

The BRAF inhibitors Dabrafenib and Vemurafenib, which have historically been used in the treatment of malignant melanoma, are now being examined for their efficacy in the treatment of lung adenoma carcinoma patients with confirmed BRAF mutations. Both inhibitors bind to forms of the oncogenic B-Raf protein with mutations at position V600E in the BRAF gene, leading to inactivation of the MAP Kinase pathway and potential apoptosis of tumor cells.[13] Rudin et al.,[14] reported the case of a 63-year-old never smoker with lung Adenocarcinoma whose mutational profile indicated an aberration in BRAF V600E. The patient was administered Dabrafenib and demonstrated a partial response as indicated by CT scan for 8 months, at which point her disease continued to progress. While initial favorable responses are generally seen with monotherapeutic inhibition of V600E variant mutated BRAF, 6-7 months of continuous dosing typically leads to drug resistance and subsequent reactivation of the MAP Kinase pathway.

As a result, the potential of therapies combining BRAF and MEK inhibition to overcome acquired resistance is beginning to gain interest. A study examining the efficacy of combination therapy for the treatment of metastatic melanoma observed a median PFS of 9.4 months in patients treated with 150mg of Dabrafenib and 2 mg of the MEK inhibitor Tremetinib compared with a median PFS of 5.4 months in patients administered Dabrafenib monotherapy.[15] An additional study comparing the PFS of melanoma patients treated with Dabrafenib-Trametinib combination therapy versus Dabrafenib monotherapy found a similar increase in PFS in patients administered combination therapy (9.3 months) over those treated with Dabrafenib alone (8.8 months).[16] In both studies the rates of adverse events were similar in the two groups examined.[15,16]

A number of MAPK-dependent mechanisms for acquired resistance to BRAF inhibitors have been proposed. Whole-exome sequencing of melanoma has linked over expression of BRAF V600E to acquired resistance of BRAF targeted therapy in melanoma.[17] Mutations which activate RAS signaling can also promote resistance to BRAF inhibition.[18] Normally, RAS signaling stimulates the dimerization and activation of RAF protein complexes. The binding of a BRAF inhibitor to one molecule in a wild type RAF dimer has been shown to stimulate the activity of the second RAF molecule resulting in up regulation of the MAPK pathway.[19] In the aforementioned case reported by Rudin et al.,[14] additional mutational profiling subsequent to the emergence of resistance revealed a novel mutation in KRAS, an upstream regulator of RAF, which was thought to be responsible for the patient's resistance. Over expression of CRAF and COT and mutations in the mitogen activated protein Kinase, MEK 1 have also been implicated in BRAF inhibitor resistance.[20-22] While these studies provide promising avenues of inquiry, further examination of the molecular mechanisms underlying resistance to BRAF inhibition is necessary.

Conclusion

Targeted therapies continue to be an encouraging alternative or supplement to traditional methods of treating various forms of cancer. Identifying molecular targets such as the RAS/RAF/MEK pathway and developing safe approaches to inhibiting their activity in cancer cells is crucial to progress in treating neoplastic disease. The use of a BRAF inhibitor coupled with an inhibitor of some other molecular target in the RAS/RAF/MEK pathway appears to be a viable treatment option for Adenocarcinoma patients with BRAF mutations who have acquired resistance to their inhibitors. At the time of this writing the patient continued to show signs of improvement for six months following the introduction of Trametinib and has tolerated the regimen with no significant side effects. For patients who have an acquired resistance to a BRAF inhibitor, further investigation into the efficacy of combining a BRAF inhibitor with therapies that inhibit alternate targets in the MAPK pathway is warranted.

Acknowledgments

None.

Conflicts of interest

Authors declare that there is no conflict of interest.

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