TITLE

Human epidermal growth factor 2 (HER2) non-small cell lung cancer (NSCLC) with YVMA mutation responsive to Ado-Trastuzumab Emtansine

SUMMARY

Human epidermal growth factor 2/NEU (HER2) aberrations account for 4.7-10% of all non-small cell lung cancers (NSCLC), making it one of the more prevalent forms of NSCLC. HER2 aberrations also instigate breast cancer and these patients commonly demonstrate a robust response to HER targeted immunotherapies. This optimistically promised that HER2 NSCLC might also respond via the same pathophysiologic mechanisms. To date, this promise has largely failed to deliver and an early trial ended in cancellation due to lack of efficacy. Contrary to this lack of efficacy, this case presents a patient with HER2 positive NSCLC with a specific gene amplification that demonstrated response to HER2 therapy. This adds to the growing evidence that targeted therapy can be efficacious in some HER2 positive NSCLC. It further reinforces the need for extended mutational testing in lung cancer patients, particularly those with a smoking history.

BACKGROUND

Human epidermal growth factor 2/NEU (HER2) aberrations account for 4.7-10% of all non-small cell lung cancers (NSCLC) [1], making it one of the more prevalent forms of NSCLC. It is most ubiquitous among non-smoking women in middle age [2]. The HER2 receptor is a membrane-bound member of the tyrosine kinase family. It interacts with a diverse array of ligands and is found in a variety of tissues [3]. HER2 aberrations also occur in approximately 15-25% of breast cancers and have been largely responsive to HER2 targeted therapies, including Ado-Trastuzumab Emtansine, an antibody drug conjugate against HER2 [4-5]. The efficacy of targeted therapy in breast cancer gave way to the hypothesis that targeted therapies would also prove effective in treating HER2 mutations in NSCLC. This hypothesis has largely failed to come to fruition, as evidenced most recently by the early termination *A Phase II Study of Trastuzumab Emtansine in HER2-Positive Non–Small Cell Lung Cancer* due to limited efficacy [6-7].

A small number of case reports document response to HER2 targeted therapies in a specific HER2 mutation with a 12 base pair insertion YVMA on exon 20 [8-11]. We present a patient with the YVMA amplification demonstrating response to HER2 therapy, adding to the accumulating evidence that targeted therapy can be efficacious in HER2 positive NSCLC.

CASE PRESENTATION

A 65-year-old lifetime non-smoking female was referred to the hematology/oncology service following evaluation for six months of cough, not productive of sputum and associated with chest wall pain. Imaging revealed a large mass in the left lower lobe measuring 7.2cm in greatest dimension and determined to be adenocarcinoma. Staging with proton emission tomography demonstrated metastatic disease. Platinum doublet therapy with Carboplatin and Paclitaxel was initiated. She underwent five complete cycles with doublet therapy before therapy was terminated due to toxicities. She was transitioned to maintenance therapy with Pemetrexed but ultimately demonstrated disease progression after two cycles.

After a short course of palliative radiation therapy, Nivolumab was initiated. After two cycles of therapy with Nivolumab, she presented to the clinic with a progressively worsening dry cough, similar to her initial presentation. She again demonstrated disease progression on chest computed tomography (CT). At this point, various treatment options were discussed with the patient. Genetic testing of her

carcinoma revealed a HER2/ERBB2 mutation at exon 20 with A775_G776insYVMA amplification. At the time of this discussion, a phase II basket trial in patients with HER2 aberrations treated with Ado-Trastuzumab Emtansine had demonstrated a 30% response rate with a few long-term responders [6]. Prior to the start of therapy with Ado-Trastuzumab Emtansine, the left lower lung mass measured 3.8 x 7.7cm on chest CT.

TREATMENT

The patient started Ado-Trastuzumab Emtansine with only hematologic side effects. A repeat chest CT two months after initiation of therapy demonstrated response with a decrease in the size of the left lower lung mass to 5.2cm in diameter, representing a 32% reduction in size. This was also associated with a decrease in the size and number of additional pulmonary nodules. She tolerated the therapy February to August 2018 without disease progression. She did require a dose reduction for thrombocytopenia.

A subsequent chest CT at nine months following the initiation of therapy re-visualized the left lung mass at 5.8cm in diameter, representing an 11% increase in size. At that time she was said to have had disease progression. She was started on immunotherapy with Pembrolizumab and was further referred for clinical trial in December 2018.

OUTCOME AND FOLLOW-UP

The patient was enrolled in a clinical trial with Poziotinib an irreversible pan-HER tyrosine kinase inhibitor with efficacy against EGFR, HER2 and HER4 [12]. She presented to the clinic for follow-up 21 months after her initial diagnosis and continues to do well in her clinical trial with stable disease.

DISCUSSION

Occasional case reports document similar response to HER2 targeted therapy in patients with genetics demonstrating the HER2 YYMA amplification on exon 20 in NSCLC. This case adds to the accruing literature demonstrating response to HER2 targeted therapy in the YVMA aberration, even in the context of trials being terminated for lack of efficacy. The subset of patients with the HER2 YVMA insertion aberrations appear to be an exception to the rule. Consequently, non-smoking patients with lung cancer should get genetic testing to determine potential responsiveness to HER2 specific therapy. Indeed, a case could be made to consider genetic testing in all patients given the results. Additionally, this adds to the growing body of literature supporting oncogene-based precision therapy for NSCLC.

LEARNING POINTS

- Despite the success heralded by HER2 positive breast cancer, HER2 positive NSCLC has been largely non-responsive to HER2 targeted therapy and has resulted in the early termination of a at least one clinical trial due to lack of efficacy
- Notwithstanding, there is growing evidence that specific mutations such as the A775_G776insYVMA amplification are favorably responsive to HER2 targeted therapy
- Consequently, extended mutational testing in lung cancer is essential in non-smokers and should be considered in all patients.

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