CLINICAL VIGNETTE

Oral Therapy for Advanced Non-Small Cell Lung Cancer

Shahryar A. Ashouri, M.D.

The patient is a 69-year-old Caucasian woman, with no previous history of smoking, who was originally diagnosed with an adenocarcinoma of the left lower lobe, six years ago. At that time, a staging PET/CT showed only localized disease, and she underwent a left lower lobe lobectomy. Pathology from the surgery showed a 1.7 x 1.5 x 1.5 cm moderately differentiated, adenocarcinoma, with no lymph node involvement, giving her a final pathologic stage of IA. Post-operatively she did well, until she developed lower back pain four years after her original surgery. A sclerotic lesion was seen in the body of L1 on plain radiographs, and therefore a PET/CT was performed for further evaluation. There was PET uptake in the L1 lesion, as well as uptake in the left, hilar lymph nodes and the previous surgical bed in the lung. A biopsy of the L1 lesion was positive for recurrent adenocarcinoma of the lung, consistent with her original diagnosis.

Given her widespread recurrence, her tumor blocks were sent for mutational analysis by PCR, and showed that she harbored a L858R point mutation in exon 21 of her Epidermal Growth Factor Receptor (EGFR) gene. Subsequently, she was started on erlotinib 150mg daily, an oral tyrosine kinase inhibitor of EGFR. Clinically her back pain and cough resolved, and a repeat PET/CT nine weeks after starting erlotinib showed a complete response. Ten weeks after starting erlotinib, she developed a severe papulopustular, acneform rash over her face and upper torso after a weekend of prolonged sun exposure (Figure 1).

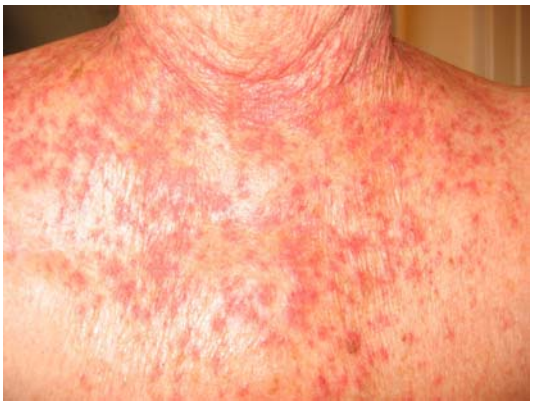

Figure 1

Her erlotinib was held, she was started on oral minocycline, topical clindamycin gel, and hydrocortisone 2.5% cream. After, three weeks her rash resolved, and she was started back on erlotinib at a reduced dose of 100mg daily. Currently, she is more than 24 months out from her recurrence with no evidence of disease on her scans.

Oral Tyrosine Kinase Inhibitors of EGFR for Stage IV Non-Small Cell Lung Cancer

Recent advances in molecular characterization of tumors have opened an era of more individualized treatments for our lung cancer patients. The era of one regimen fitting all cases of non-small cell lung cancer (NSCLC) is coming to an end. Among these promising pathways is the epidermal growth factor receptor (EGFR) signaling cascade, a member of the ErbB family of cell membrane receptors. EGFR (also known as ErbB-1 and HER-1) signaling in NSCLC has been shown to lead to tumor cell proliferation and tumor cell survival[1,2]. In preclinical models, shutting down this signaling pathway, has led to increased tumor cell death through apoptosis[2].

EGFR has an extracellular domain that recognizes and binds ligands, a hydrophobic transmembrane domain involved in dimerization, and an intracellular domain with tyrosine kinase activity. Receptor dimerization leads to phosphorylation of tyrosine residues in the kinase domain, which then trigger downstream signal transduction, eventually leading to induction of cell proliferation, protection from apoptosis, activation of angiogenesis, and development of metastasis[3-5]. Specific activating mutations within the tyrosine kinase domain of EGFR have been identified in small sub-groups of patients with NSCLC[6]. Mutations in the kinase domain of EGFR gene occur at a frequency of about 10% of patients in the United States, but, in 30-50% of people of East Asian descent[7].

The U.S. Food and Drug Administration (FDA) approved the first EGFR tyrosine kinase inhibitor (TKI), gefitinib, in NSCLC on May 5, 2003 for third line therapy. Unfortunately, the phase III placebo-controlled study comparing gefitinib to best supportive care in a heterogeneous population of previously treated patients with NSCLC, did not show a statistically significant prolongation in overall survival, and its use was shortly restricted in the U.S.[8]. However, in sub-group analysis of Asian and never-smoker groups, both of which have been associated with higher rates of activating EGFR mutations, there were statistically significant overall survival seen in the gefitinib treated groups[8]. In a parallel phase III, randomized, double-blinded, placebo-controlled trial with erlotinib in previously treated NSCLC patients, there was a significant overall survival and progression free survival in patients who received the TKI[9]. Therefore, a second reversible oral TKI of EGFR, erlotinib, was approved by the FDA in 2004[9].

Subgroup analysis from these initial trials, showed that a specific phenotype of patient (adenocarcinoma, East Asian descent, women, no history of smoking) who received erlotinib or gefitinib had higher rates of success in terms of response rates and survival[8,9]. Furthermore, these physical characteristics may be unmasking specific EGFR mutations leading to constitutive activation of signal transduction, and therefore hypersensitivity to TKI's such as erlotinib and gefitinib[6,10]. Due to these findings, oral TKI's were taken to the first line setting, in these highly selected patient groups.

Traditionally, in advanced NSCLC, a response rate of 20-35% with cytotoxic, chemotherapy doublets, with or without an angiogenesis inhibitor (bevacizumab) in the frontline setting has been well documented, with a median overall survival of approximately 10 to 12 months[11,12]. However, response rates of more than 70% were seen in the frontline treatment of patients harboring activating EGFR mutations[10]. This correlated to a median overall survival of 27 months, a number not previously seen in stage IV lung cancer[10]. Due to these results, patients harboring EGFR mutations could be effectively treated with an oral TKI, with both better efficacy and less side effects when compared to traditional cytotoxic chemotherapy.

Adverse effects of EGFR TKI's, such as erlotinib, include rash and diarrhea. In clinical trials, diarrhea was the dose limiting toxicity of this class of agents, affecting up to half of patients. Clinically severe diarrhea affected approximately 6% of treated patients[13]. Therapy should be stopped if severe diarrhea develops, and loperamide can be used to control output. Once resolved, therapy can be reinstated.

Some degree of rash has been reported in up to 76% of patients who received EGFR TKI's[14]. This is generally described as a papulopustular rash involving the face and upper torso. Median onset of rash is 1-3 weeks after initiation of treatment, and usually lasts up to two weeks. Pathogenesis of EGFR inhibitor induced, cutaneous

toxicity in not completely understood. Eight to twelve percent of patients develop severe rash, requiring interruption of therapy. Various topical and systemic combinations of antibiotics and glucocorticoids have been used for relief. Upon resolution of severe rashes, dose adjustment is recommended prior to re-initiating TKI. Pre-emptive, rather than reactive, strategies have also been successfully implemented using moisturizers, sun screen, topical corticosteroids, and doxcycline[14].

Compared to traditional cytotoxic agents used in NSCLC, oral EGFR TKI's, such as erlotinib, appear to be much more tolerable, and efficacious in an identifiable subgroup of patients diagnosed with this disease.

REFERENCES

1. **Cappuzzo F, Magrini E, Ceresoli GL, Bartolini S, Rossi E, Ludovini V, Gregorc V, Ligorio C, Cancellieri A, Damiani S, Spreafico A, Paties CT, Lombardo L, Calandri C, Bellezza G, Tonato M, Crinò L**. Akt phosphorylation and gefitinib efficacy in patients with advanced non-small-cell lung cancer. *J Natl Cancer Inst*. 2004 Aug 4;96(15):1133-41.
2. **Herbst RS, Heymach JV, Lippman SM**. Lung cancer. *N Engl J Med*. 2008 Sep 25;359(13):1367-80. Review.
3. **Salomon DS, Brandt R, Ciardiello F, Normanno N**. Epidermal growth factor-related peptides and their receptors in human malignancies. *Crit Rev Oncol Hematol*. 1995 Jul;19(3):183-232. Review.
4. **Yarden Y, Sliwkowski MX**. Untangling the ErbB signalling network. *Nat Rev Mol Cell Biol*. 2001 Feb;2(2):127-37. Review.
5. **Zhang X, Gureasko J, Shen K, Cole PA, Kuriyan J**. An allosteric mechanism for activation of the kinase domain of epidermal growth factor receptor. *Cell*. 2006 Jun 16;125(6):1137-49.
6. Lynch TJ, Bell DW, Sordella R, Gurubhagavatula S, **Okimoto RA, Brannigan BW, Harris PL, Haserlat SM, Supko JG, Haluska FG, Louis DN, Christiani DC, Settleman J, Haber DA**. Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. *N Engl J Med*. 2004 May 20;350(21):2129-39. Epub 2004 Apr 29.
7. **Sequist LV, Martins RG, Spigel D, Grunberg SM, Spira A, Jänne PA, Joshi VA, McCollum D, Evans TL, Muzikansky A, Kuhlmann GL, Han M, Goldberg JS, Settleman J, Iafrate AJ, Engelman JA, Haber DA, Johnson BE, Lynch TJ**. First-line gefitinib in patients with advanced non-small-cell lung cancer harboring somatic EGFR mutations. J Clin Oncol. 2008 May 20;26(15):2442-9. Epub 2008 May 5. Erratum in: *J Clin Oncol*. 2008 Jul 10;26(20):3472.
8. **Thatcher N, Chang A, Parikh P, Rodrigues Pereira J, Ciuleanu T, von Pawel J, Thongprasert S, Tan EH, Pemberton K, Archer V, Carroll K**. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small-cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet*. 2005 Oct 29-Nov 4;366(9496):1527-37.
9. **Shepherd FA, Rodrigues Pereira J, Ciuleanu T, Tan EH, Hirsh V, Thongprasert S, Campos D, Maoleekoonpiroj S, Smylie M, Martins R, van Kooten M, Dediu M, Findlay B, Tu D, Johnston D, Bezjak A, Clark G, Santabárbara P, Seymour L**; National Cancer Institute of Canada Clinical Trials Group. Erlotinib in previously treated non-small-cell lung cancer. *N Engl J Med*. 2005 Jul 14;353(2):123-32.
10. **Rosell R, Moran T, Queralt C, Porta R, Cardenal F, Camps C, Majem M, Lopez-Vivanco G, Isla D, Provencio M, Insa A, Massuti B, Gonzalez-Larriba JL, Paz-Ares L, Bover I, Garcia-Campelo R, Moreno MA, Catot S, Rolfo C, Reguart N, Palmero R, Sánchez JM, Bastus R, Mayo C, Bertran-Alamillo J, Molina MA, Sanchez JJ, Taron M**; Spanish Lung Cancer Group. Screening for epidermal growth factor receptor mutations in lung cancer. *N Engl J Med*. 2009 Sep 3;361(10):958-67. Epub 2009 Aug 19.
11. **Schiller JH, Harrington D, Belani CP, Langer C, Sandler A, Krook J, Zhu J, Johnson DH**; Eastern Cooperative Oncology Group. Comparison of four chemotherapy regimens for advanced non-small-cell lung cancer. *N Engl J Med*. 2002 Jan 10;346(2):92-8.
12. **Sandler A, Gray R, Perry MC, Brahmer J, Schiller JH, Dowlati A, Lilenbaum R, Johnson DH**. Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med. 2006 Dec 14;355(24):2542-50. Erratum in: *N Engl J Med*.2007 Jan 18;356(3):318.
13. **Cataldo VD, Gibbons DL, Pérez-Soler R, Quintás-Cardama A**. Treatment of non-small-cell lung cancer with erlotinib or gefitinib. *N Engl J Med*. 2011 Mar 10;364(10):947-55. Review.
14. **Thatcher N, Nicolson M, Groves RW, Steele J, Eaby B, Dunlop J, McPhelim J, Nijjar R, Ukachukwu I; U.K**. Erlotinib Skin Toxicity Management Consensus Group. Expert consensus on the management of erlotinib-associated cutaneous toxicity in the u.k. *Oncologist*. 2009 Aug;14(8):840-7. Epub 2009 Aug 13.

Submitted on March 31, 2011