Editorial

Management of stage IA *EGFR*-mutant adenocarcinoma of the lung

Robert Pirker

Department of Medicine I, Medical University of Vienna, Vienna, Austria

Correspondence to: Robert Pirker, MD. Professor of Medicine, Department of Medicine I, Medical University of Vienna, Währinger Gürtel 18-20, 1090 Vienna, Austria. Email: robert.pirker@meduniwien.ac.at.

Comment on: Zhang Y, Shen J, Simone CB 2nd, *et al.* How to optimize the treatment strategy for patients with EGFR-mutant stage IA lung adenocarcinoma: an international multidisciplinary team. J Thorac Dis 2018;10:3883-90.

Submitted Aug 08, 2018. Accepted for publication Aug 13, 2018.
doi: 10.21037/jtd.2018.08.70
View this article at: http://dx.doi.org/10.21037/jtd.2018.08.70

In a recent article, a multidisciplinary team of international experts discussed the diagnostic and therapeutic management of a 44-year-old male never-smoker with early-stage adenocarcinoma of the lung (1). The patient had suffered from cough and was diagnosed with clinical stage IA of an adenocarcinoma in the middle lobe of the right lung. He underwent lobectomy of the right middle lobe and mediastinal lymph node sampling. Pathological tumor stage IA and adenocarcinoma histology were confirmed. Molecular analysis of the tumor tissue detected an epidermal growth factor receptor (*EGFR*) exon 19 deletion. Adjuvant treatment with erlotinib was initiated. After 6 months, however, the patient decided to discontinue treatment. Nearly 2 years after discontinuation of erlotinib, the patient developed pain in the thoracic vertebrae and two metastases of the thoracic vertebrae were diagnosed by magnetic resonance (MR) imaging. The patient underwent surgery and pathological analyses confirmed adenocarcinoma of the lung with *EGFR* exon 19 deletion. The patient was then re-treated with erlotinib.

Based on this patient, diagnostic and therapeutic options for patients with early-stage adenocarcinomas of the lung were discussed by experts (1). Management may be affected by the treating physician, expertise of the center, access as well as affordability of treatments, and other factors. The actual treatment of the patient described in the article was individualized and arguments for treatment decisions were provided. Here I will describe how I would have managed this patient.

In my opinion, the patient underwent perfect pre-operative staging that included positron emission tomography-computer tomography (PET-CT), MR imaging of the brain, and transbronchial lung biopsy. Pathological examination was extensive and revealed lung adenocarcinoma with an *EGFR* exon 19 deletion. The tumor was classified as cT1aN0M0 and stage IA according to the 7th edition of the TNM classification for lung cancer in use at the time of diagnosis. According to the current 8th edition (2), the tumor is classified as cT1bN0M0, because the tumor lesion measured approximately 1.4 cm, and as stage IA2.

I fully agree with the decision to undergo surgery with curative intent in this rather young patient. Surgery immediately removes the tumor, allows exact pathological tumor staging, provides sufficient tumor material for pathological examination including molecular analyses, and also avoids difficulties in interpretation of potential radiological changes in the lung during follow-up. Patients undergoing stereotactic radiotherapy sometimes develop changes in the lung that are difficult to be differentiated between tumor relapse and radiotherapy-associated toxicity. In agreement with the experts, I recommend stereotactic radiotherapy of lung cancer primarily for elderly patients, patients with poor performance status, and those who prefer stereotactic radiotherapy over surgery. However, I do acknowledge that surgeons and radio-oncologists may sometimes disagree on the type of preferred local treatment of early-stage non-small cell lung cancer (NSCLC).

After complete resection of the tumor, the question arises whether the patient should undergo adjuvant systemic treatment. In my opinion, observation without any adjuvant therapy is the current standard for a patient with completely resected adenocarcinoma and pathological tumor stage IA. Therefore, I would recommend this strategy to the patient

under discussion. While patients with *EGFR*-mutant NSCLC are also candidates for adjuvant chemotherapy (like patients with *EGFR* wild-type tumors), adjuvant chemotherapy is currently only recommended for patients with tumor stages II–III (3). Based on a meta-analysis, adjuvant chemotherapy may be detrimental for patients with stage IA (3). Thus, adjuvant chemotherapy is not an option for the patient under discussion.

A more difficult to answer question is whether the patient should be offered adjuvant therapy with an EGFR tyrosine kinase inhibitor (TKI) because of the presence of an *EGFR* exon 19 deletion in the tumor. My answer to this question is no for several reasons. Firstly, phase 3 trials on adjuvant therapy with EGFR TKIs did not enroll patients with stage IA disease (4-6). Secondly, two phase 3 trials failed to demonstrate a benefit for adjuvant EGFR TKIs on unselected patients or patients selected based on EGFR protein expression (4,5). Thirdly, the Chinese phase 3 trial demonstrated an improved progression-free survival for gefitinib compared to chemotherapy with cisplatin plus vinorelbine among patients with stage II–IIIA NSCLC but did not provide data on overall survival (6). Taken together, therefore, the efficacy of adjuvant EGFR TKIs in terms of overall survival has not been proven and, in particular, these drugs have not been studied in patients with completely resected stage IA NSCLC. In the potential scenario that the patient urgently asks for adjuvant therapy, however, I might consider treatment with an EGFR TKI. In this case, I would choose gefitinib because of its lower skin toxicity and proven efficacy in the Chinese trial among patients with tumor stages II–IIIA (6). Tolerance is an important issue with EGFR TKIs as adjuvant therapy because they are planned to be administered over prolonged periods. Although treatment was planned for two years, median duration of treatment with erlotinib was only 11.9 months among RADIANT patients (5). Consistent with this low treatment compliance, the patient under discussion discontinued erlotinib treatment after six months.

About two and a half years after initial diagnosis, the patient developed back pain due to bone metastases. This relapse is somewhat surprising because patients with pathological stage IA NSCLC have good prognosis with 5-year survival rates reaching about 90% (2). Bone metastases are common, often associated with pain, and usually confirmed by MR imaging. Due to the development of systemic metastases, further treatments will be with palliative intent in the patient under discussion. In agreement with the experts, I recommend palliative radiotherapy to the symptomatic bone lesions. Systemic treatment with denosumab should also be considered. Prior to radiotherapy, an orthopedic surgeon should examine the patient and in co-operation with a neuro-surgeon should decide whether surgery of the bone lesions is required for symptom relief and/or prevention of future complications. The patient under discussion underwent surgery but did not receive palliative radiotherapy to the bone lesions.

The question now arises whether the patient should receive systemic treatment in addition to local treatment of the bone lesions. The experts agreed on systemic re-treatment with an EGFR TKI (1). I agree with this strategy. I order liquid biopsy at the time of disease progression in patients who have undergone treatment with EGFR TKIs for *EGFR* mutation-positive NSCLC (7). If liquid biopsy is negative or inconclusive for T790M, tissue biopsy should be considered if it is deemed feasible and safe for the patient. In patients with metastases to the vertebra, I rarely go for tissue biopsy.

If T790M mutation is detected by liquid biopsy and/or tumor tissue analysis, I treat with osimertinib until disease progression. If T790M is not proven for whatever reason, several treatment options do exist. I would treat with afatinib because as a second-generation EGFR TKI it may still have efficacy in patients pre-treated with a first-generation EGFR TKIs, particularly in case of exon 19 deletion. Chemotherapy may be another option, although I have some doubts about its efficacy in patients who primarily present with bone metastases. Immune checkpoint inhibitors may be less active in patients with *EGFR* mutation-positive NSCLC and, in my opinion, should be considered later during the course of the disease. Observation after palliative radiotherapy may also be an option, although the young age of the patient speaks against this option. The patient under discussion opted for re-treatment with erlotinib.

I agree with the authors that international multidisciplinary teams can play an important role in the management of patients with lung cancer. They allow scientific and medical exchange among world experts. This is particularly important for lung cancer because it is a global disease with regional differences. These teams can also enhance international education and co-operation.

In conclusion, the patient with early-stage adenocarcinoma of the lung did allow an interesting discussion of the various treatment options in patients with NSCLC. Case discussion like this should be encouraged because of their educational value. Continuous medical education is crucial at a time of

rapidly diagnostic and therapeutic advances in lung cancer.

Acknowledgements

None.

Footnote

Conflicts of Interest: R Pirker has received honoraria for serving as a member of the Data Monitoring Committee from Merck Sharp Dohme, Genmab and Regeneron and has received consulting fees and/or speaker's fees from AstraZeneca, Boehringer Ingelheim and Eli Lilly.

References

1. Zhang Y, Shen J, Simone CB 2nd, et al. How to optimize the treatment strategy for patients with EGFR-mutant stage IA lung adenocarcinoma: an international multidisciplinary team. J Thorac Dis 2018;10:3883-90.
2. Goldstraw P, Chansky K, Crowley J, et al. The IASLC Lung Cancer Staging Project: Proposals for Revision of the TNM Stage Groupings in the Forthcoming (Eighth) Edition of the TNM Classification for Lung Cancer. J Thorac Oncol 2016;11:39-51.
3. Pignon JP, Tribodet H, Scagliotti GV, et al. Lung adjuvant cisplatin evaluation: a pooled analysis by the LACE Collaborative Group. J Clin Oncol 2008;26:3552-9.
4. Goss GD, O'Callaghan C, Lorimer I, et al. Gefitinib versus placebo in completely resected non-small-cell lung cancer: results of the NCIC CTG BR19 study. J Clin Oncol 2013;31:3320-6.
5. Kelly K, Altorki NK, Eberhardt WE, et al. Adjuvant Erlotinib Versus Placebo in Patients With Stage IB-IIIA Non-Small-Cell Lung Cancer (RADIANT): A Randomized, Double-Blind, Phase III Trial. J Clin Oncol 2015;33:4007-14.
6. Zhong WZ, Wang Q, Mao WM, et al. Gefitinib versus vinorelbine plus cisplatin as adjuvant treatment for stage II-IIIA (N1-N2) EGFR-mutant NSCLC (ADJUVANT/CTONG1104): a randomised, open-label, phase 3 study. Lancet Oncol 2018;19:139-48.
7. Buder A, Hochmair MJ, Schwab S, et al. Cell-Free Plasma DNA-Guided Treatment With Osimertinib in Patients With Advanced EGFR-Mutated NSCLC. J Thorac Oncol 2018;13:821-30.

Cite this article as: Pirker R. Management of stage IA *EGFR*-mutant adenocarcinoma of the lung. J Thorac Dis 2018;10(Suppl 26):S3260-S3262. doi: 10.21037/jtd.2018.08.70

