Editorial

Individualizing adjuvant therapy for early stage non-small cell lung cancer: we see the destination, but we don't yet know the route

Howard West

Thoracic Oncology Program, Swedish Cancer Institute, Seattle, WA 98104, USA

Correspondence to: Howard West, MD. Medical Director, Thoracic Oncology Program, Swedish Cancer Institute, 1221 Madison Street, Suite 200, Seattle, WA 98104, USA. Email: howard.west@swedish.org.

Submitted Dec 27, 2014. Accepted for publication Dec 30, 2014.

doi: 10.3978/j.issn.2072-1439.2015.01.08

View this article at: http://dx.doi.org/10.3978/j.issn.2072-1439.2015.01.08

Though the survival benefit of adjuvant therapy for at least stage II-IIIA non-small cell lung cancer (NSCLC) has been demonstrated in multiple prospective randomized phase III trials, we should recognize that our approach to post-operative management of early stage NSCLC is relatively primitive. In hopes of curing more patients, we recommend a challenging, toxic therapy to all fit patients, despite understanding that many should already be cured with no further therapy. Moreover, we can readily appreciate that platinum-based doublet therapy is far more effective for some patients than for others and that, as we have now entered an era of molecularly-guided oncology treatment, specific targeted therapies may be far superior to conventional chemotherapy for prospectively identified populations.

In order to optimize delivery of adjuvant therapy in early stage NSCLC, we should hope to be able to answer two critical questions:

(I) Is this particular patient in question at sufficient risk of recurrence to justify the acute and chronic toxicity risks of adjuvant therapy?

(II) What is the most effective therapy we can offer to maximize long-term survival for this specific patient?

Both questions necessitate moving beyond conventional, anatomy-based cancer staging and a "one-size-fits-all" approach to adjuvant therapy. Are we ready to offer adjuvant therapy today or imminently with such an informed strategy? Unfortunately, the recent publication of the French Tailored Post-Surgical Therapy in Early Stage (TASTE) NSCLC trial by Wislez and colleagues, a phase II study that randomized patients between customized adjuvant therapy recommendations and a standard, default approach (1) serves to highlight our limitations in hoping to execute such a plan.

The TASTE trial randomized 150 fit patients with stage II-IIIA non-squamous NSCLC from 29 French cancer centers to receive either a standard therapy arm of up to four cycles of post-operative cisplatin/pemetrexed or a customized approach that recommended treatment based on the presence or absence of an activating mutation in the epidermal growth factor receptor (EGFR) gene, its presence associated with a very high probability of prolonged response to EGFR tyrosine kinase inhibitor (TKI) therapy (2), as well as tumor expression of the excision repair cross-complementation group 1 (ERCC-1) protein as assessed by immunohistochemistry (IHC), which has been associated with decreased efficacy of platinum-based chemotherapy in the settings of adjuvant (3) and metastatic NSCLC (4). Specifically, customized adjuvant therapy was assigned based on these results, such that EGFR mutation-positive patients were assigned to receive a year of EGFR TKI erlotinib, those with ERCC-1 negative tumors were designated to receive up to four cycles of cisplatin/pemetrexed, and those EGFR mutation-negative patients with ERCC-1 positive tumors were assigned to receive no adjuvant therapy. The primary endpoint was feasibility of timely testing and initiation of protocol-directed treatment based on biomarker results, within the first 60 days after surgery. Pending favorable completion of the phase II portion, a much larger phase III trial with the same overall design would ensue.

While the study did management to barely meet this criterion, the authors detected a discrepancy between the expected rate of ERCC-1 positivity based on prior work (3)

of 44% and that seen in the current phase II experience, at only 26%. This led to an examination of the 8F1 antibody and re-evaluation of tumor tissue using different versions of the antibody, illustrating a discordance and unreliability of the assay that led to the discontinuation of the phase II trial and the planned phase III effort.

Where does this experience leave us? The authors deserve to be congratulated for conducting a coordinated multi-center trial that managed to direct four out of five patients onto a biomarker-informed adjuvant therapy in a very time-limited fashion. The unreliability of ERCC-1 IHC undermined this effort, but we must also recognize that the value of such a tailored strategy is predicated on a clearly superior recommended treatment based on its results. Recent publications of several prospective randomized trials of biomarker-directed chemotherapy selection have demonstrated no benefit in terms of response rate or survival for individualized treatment based on these poorly validated biomarkers in the metastatic setting (5,6). Even in the setting of activating EGFR mutation-positive advanced NSCLC, where EGFR TKI therapy is so consistently superior to conventional chemotherapy as first-line therapy (2), the value of EGFR TKI therapy in the adjuvant setting for EGFR mutation-positive patients has been demonstrated in terms of disease-free survival but not yet in terms of overall survival (7,8) and remains an open question.

We are in the midst of a profound change in our practice, in which genomic testing, with the availability of broad multiplex biomarker evaluation now commercially available and becoming integrated increasingly into clinical trials and practice patterns. The results from the TASTE and advanced NSCLC trials highlight that our biomarker-driven hypotheses remain unvalidated and require prospective testing before we presume that early results will invariably translate to substantial clinical gains that will be confirmed in more careful testing. We should hope and expect that genomic testing will yield promising leads that withstand scrutiny from prospective testing and become the paths to further gains in the advanced disease setting, ideally also helping to guide our selection of standard chemotherapy agents, in addition to molecularly targeted treatments and immunotherapies. Only after we gain clear insights from the more readily accessible advanced disease setting are we likely to be able to transpose these individualized treatment approaches into the setting of early stage disease, a setting in which results are deferred for years and are diluted by the proportion of patients destined for cure regardless of post-operative interventions.

It is easy to envision a far superior approach to adjuvant therapy, in which we can better distinguish the patients who truly need further therapy by using genomics-informed panels and molecular signatures, such as recently reported assays that have shown early promise (9,10), and especially that we can deliver the promise of personalized cancer therapy to the curative setting of early stage NSCLC. For now, however, we must be patient to learn the right route to our ultimate destination.

Acknowledgements

Disclosure: The author declares no conflict of interest.

References

1. Wislez M, Barlesi F, Besse B, et al. Customized adjuvant phase II trial in patients with non-small-cell lung cancer: IFCT-0801 TASTE. J Clin Oncol 2014;32:1256-61.
2. Paz-Ares L, Soulières D, Moecks J, et al. Pooled analysis of clinical outcome for EGFR TKI-treated patients with EGFR mutation-positive NSCLC. J Cell Mol Med 2014;18:1519-39.
3. Olaussen KA, Dunant A, Fouret P, et al. DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 2006;355:983-91.
4. Lord RV, Brabender J, Gandara D, et al. Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 2002;8:2286-91.
5. Bepler G, Williams C, Schell MJ, et al. Randomized international phase III trial of ERCC1 and RRM1 expression-based chemotherapy versus gemcitabine/carboplatin in advanced non-small-cell lung cancer. J Clin Oncol 2013;31:2404-12.
6. Moran T, Wei J, Cobo M, et al. Two biomarker-directed randomized trials in European and Chinese patients with nonsmall-cell lung cancer: the BRCA1-RAP80 Expression Customization (BREC) studies. Ann Oncol 2014;25:2147-55.
7. Pennell NA, Neal JW, Chaft JE, et al. SELECT: A multicenter phase II trial of adjuvant erlotinib in resected early-stage EGFR mutation-positive NSCLC. J Clin Oncol 2014;32(5s): abstr 7514.
8. Shepherd FA, Altorki NK, Eberhardt WE, et al. Adjuvant erlotinib (E) versus placebo (P) in non-small cell lung cancer (NSCLC) patients (pts) with tumors carrying EGFR-sensitizing mutations from the RADIANT trial. J Clin Oncol 2014;32(5s):abstr 7513.

9. Kratz JR, He J, Van Den Eeden SK, et al. A practical molecular assay to predict survival in resected non-squamous, non-small-cell lung cancer: development and international validation studies. Lancet 2012;379:823-32.
10. Wistuba II, Behrens C, Lombardi F, et al. Validation of a proliferation-based expression signature as prognostic marker in early stage lung adenocarcinoma. Clin Cancer Res 2013;19:6261-71.

Cite this article as: West H. Individualizing adjuvant therapy for early stage non-small cell lung cancer: we see the destination, but we don't yet know the route. J Thorac Dis 2015;7(3):235-237. doi: 10.3978/j.issn.2072-1439.2015.01.08

