Lung Cancer xxx (2015) xxx–xxx

Contents lists available at ScienceDirect

Lung Cancer

journal homepage: www.elsevier.com/locate/lungcan

Review

Adjuvant therapy for EGFR mutant and ALK positive NSCLC: Current data and future prospects

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ARTICLE INFO

Article history:
Received 22 July 2015
Accepted 27 July 2015

Keywords:
Non-small cell lung cancer (NSCLC)
Anaplastic lymphoma kinase (ALK)
Epidermal growth factor receptor (EGFR)
Adjuvant
Tyrosine kinase inhibitors (TKI)

ABSTRACT

Tyrosine kinase inhibitors (TKIs) against targetable mutations such as epidermal growth factor receptor (EGFR) and anaplastic lymphoma kinase (ALK) are highly effective in treating advanced stage lung cancers harboring such mutations. Questions remain, however, about whether these agents can improve cure rates for early stage lung cancers in the adjuvant setting. Here, we examine the current data and ongoing trials addressing this issue.

1. Background

Lung cancer remains a formidable diagnosis even when identified in the earliest stages. Median 5-year survival rate (a surrogate for cure rate) for local and locally advanced non-small cell lung cancer (NSCLC) ranges from 51% for stage IA disease to 26% for stage IIIA disease [1], lower than that seen in breast [2], prostate [3], or colorectal cancers [4]—the other most common cancers in developed countries.

Complete surgical resection remains the most effective initial therapy for patients with early stage NSCLC. The LACE Collaborative Group meta-analysis of five large adjuvant chemotherapy trials showed that post-operative cisplatin-based chemotherapy significantly improved survival in patients with resected NSCLC, with a 5-year absolute overall survival (OS) benefit of 5.4%. The benefit varied with stage, with a stronger effect observed with increasing stage (hazard ratio (HR) for stage IA = 1.40 with 95% confidence interval (CI) = 0.95–2.06; HR for stage IB = 0.93, 95% CI = 0.78–1.10; HR for stage II = 0.83, 95% CI = 0.73–0.95; and HR for stage III = 0.83, 95% CI = 0.72–0.94) [5]. Subsequently, the NSCLC Meta-analyses Collaborative Group performed a pooled outcome analysis on an even larger number of patients included on adjuvant trials, and similarly demonstrated that the addition of adjuvant chemotherapy improved survival after surgery with an absolute increase in survival of 4% at 5 years [6]. Based on the above studies, all major guidelines currently recommend cisplatin-based chemotherapy regimen after surgical resection for patients stage II and III NSCLC and for certain patients with stage IB with tumors over 4 cm. However, the benefit for earlier stage I patients and the efficacy of carboplatin or non-platinum containing chemotherapy regimens remains uncertain.

2. TKI for metastatic NSCLC

Treatments for lung cancers have greatly advanced in the last decade, following the observation that tumors with oncogenic driver mutations, such as epidermal growth factor receptor (EGFR) mutations or anaplastic lymphoma kinase (ALK) rearrangements, can respond dramatically to selected targeted therapies.

Compared with first-line chemotherapy treatment, patients with advanced stage NSCLC harboring EGFR mutations have higher response and longer progression free survival (PFS) when treated with EGFR targeted TKIs. Gefitinib was found to result in a superior PFS compared with carboplatin/paclitaxel in patients with advanced NSCLC with EGFR mutations in the IPASS study [7,8] and additional trials [9,10]. Erlotinib was compared to chemotherapy in EGFR mutant NSCLC in two randomized trials. In the OPTIMAL trial erlotinib demonstrated a superior PFS compared to carboplatin/gemcitabine (13.1 months vs. 4.6 months, HR 0.16, 95% CI = 0.10–0.26; $p < 0.0001$). [11] The EURTAC trial compared erlotinib with platinum-based chemotherapy doublet, and showed increased PFS, though no difference in OS, possibly due to high

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http://dx.doi.org/10.1016/j.lungcan.2015.07.016
0169-5002/

cross-over [12]. Lastly, afatinib was compared to chemotherapy as first line therapy for advanced EGFR mutant NSCLC in two phase III trials. LUX-Lung 3 trial compared afatinib with cisplatin/pemetrexed, with increased PFS in the afatinib arm [13,14]. LUX-Lung 6 trial compared afatinib with cisplatin/gemcitabine, and also showed increased PFS in the afatinib arm (11.0 months vs. 5.6 months) [15]. In an analysis of both LUX-Lung 3 + 6, there was also a significant improvement in OS favoring the afatinib arm, an effect that appeared restricted to the EGFR exon 19 deletion subgroup [16,17].

Similarly, tumors with activating ALK gene rearrangements respond favorably to ALK-targeted TKIs in the advanced stage setting. Crizotinib was superior to standard second-line chemotherapy (pemetrexed or docetaxel) in patients with advanced NSCLC with ALK rearrangement (PFS 7.7 months for crizotinib vs. 3.0 months for chemotherapy, HR 0.49, 95% CI = 0.37–0.64) [18]. As first-line therapy, crizotinib is also superior to standard chemotherapy (pemetrexed plus either cisplatin or carboplatin) [19]. Second generation TKIs of ALK are showing promise. Ceritinib is approved by the US FDA in crizotinib-refractory or intolerant patients based on an overall response rate of 54.6% (95% CI = 47–62) and median duration of response of 7.4 months (95% CI = 5.1–10.1) in this setting. [20,21] It is being compared to chemotherapy both after progression on a platinum-based doublet (NCT01828112) and as first line treatment (NCT01828099) in two phase III trials that are currently recruiting. Alectinib also is quite effective after crizotinib failure, and is being tested against chemotherapy, as well as head-to-head with crizotinib in a separate trial, for patients with ALK-positive advanced NSCLC [22–24]. Another new addition is brigatinib, which has promising antitumor activity in ALK+ NSCLC patients with and without prior crizotinib, including those with brain metastases. Of the 72 evaluable patients, 52 (72%) responded: 45/65 (69%) patients with prior crizotinib and 7/7 crizotinib-naive patients [25]. Multiple agents with activity against ALK translocated lung cancer are in development.

It is worth noting that though most TKIs are well tolerated, with effective supportive medications if needed, they can still come with potential serious side effects. All TKIs appear to cause fatigue, which is usually mild but can necessitate dose reduction if intolerable. Rash and diarrhea are common with EGFR TKIs, and potential fatal pulmonary and hepatic toxicities have been reported [26]. Gastrointestinal side effects including anorexia, diarrhea, nausea and vomiting are sometimes observed with crizotinib and are more frequent with ceritinib, and potentially fatal hepatotoxicity and thrombocytopenia have been reported [27]. It is also important to note that while a very small minority of patients have long-term disease stability on EGFR TKIs after initial response, progression is nearly inevitable, usually in less than 1 year.

3. Rationale for Adjuvant TKI for Early Stage NSCLC

The goal of treatment in early stage lung cancer is cure without long-term therapy related complications. With the successful integration of TKIs in the treatment of advanced NSCLC with targetable mutations, and further promising results from ongoing trials, it is only reasonable to wonder whether we can extend this benefit to early stage NSCLC and actually improve long-term survival rates for these patients. This is an important question as recurrence rates after complete surgical resection followed by appropriate adjuvant therapies still remains as high as 70% [5].

As described earlier, adjuvant chemotherapy improves the survival after surgical resection by 4–5% at the 5 year mark, which is a surrogate for "cure" since NSCLC rarely recurs after this interval [5,6]. For patients who are able to tolerate more therapy, addition of adjuvant TKI after completion of the standard adjuvant chemotherapy is a very reasonable question to study. Another area worth investigating is whether adjuvant TKI would increase cure for patients with early stage NSCLC who do not require adjuvant chemotherapy after complete surgical resection.

Commonly, patients may be ineligible for chemotherapy due to other co-morbid conditions, or decline the toxicity of chemotherapy after undergoing a major surgery for the lung cancer resection. An oral agent with potentially better tolerability profile may be an attractive option for these patients. Effectiveness of adjuvant TKI in this setting is also being investigated (see Section 6).

It is also worth noting that success with adjuvant TKIs has been observed in other tumor types. Adjuvant imatinib improves recurrence-free survival and OS of gastrointestinal stromal tumor (GIST) patients with a high risk of GIST recurrence [28]. In addition, for patients with HER-2 positive early breast cancer, 1 year of treatment with the HER-2 targeted antibody trastuzumab after adjuvant chemotherapy has a significant OS benefit after a median follow-up of 2 years [29].

4. Existing data for adjuvant TKI use

Several trials have examined the use of EGFR TKIs in both unselected patients and selected patients with EGFR mutations in the adjuvant setting.

4.1. Retrospective studies

A retrospective analysis of patients from the Memorial Sloan Kettering Cancer Center (MSKCC) examined whether TKI use improves outcomes in patients with early stage EGFR mutated lung cancer after resection [30]. The cohort consisted of patients with completely resected stages I–III lung adenocarcinoma harboring activating EGFR exon 19 or 21 mutations. Ninety-three patients (56%) had exon 19 deletion, 74 patients (44%) had exon 21 mutations, and 56 patients (33%) received perioperative TKI. As this was a retrospective review the patients were not randomized. In a multivariate analysis controlling for sex, stage, type of surgery, and adjuvant platinum chemotherapy, the 2-year disease free survival (DFS) was 89% for patients treated with adjuvant TKI compared with 72% in the group who did not receive an EGFR TKI (HR 0.53; 95% CI: 0.28–1.03; $p = 0.06$). The 2-year OS was 96% with adjuvant EGFR TKI and 90% in the group that did not receive TKI (HR 0.62; 95% CI: 0.26–1.51; $p = 0.296$). There was a trend toward improvement in DFS among this cohort of patients who received TKIs as adjuvant therapy, though results were not statistically significant and the study was limited by being a non-randomized retrospective analysis.

A retrospective Chinese study by Lv et al. suggests a DFS but not OS benefit of adjuvant EGFR TKI in patients harboring EGFR mutations after complete surgical resection. The authors identified 257 patients (stage I-126; stage II–IIIa-131) who had complete surgical resections and EGFR testing and identified 138 patients with EGFR mutated disease. EGFR mutation status was unrelated to recurrence (HR = 0.83; 95% CI = 0.572–1.204; $P = 0.326$) or death (HR = 0.679; 95% CI = 0.406–1.136; $P = 0.14$). Thirty-one patients with EGFR mutant resected lung cancer received adjuvant EGFR-TKIs; 27/31 (87.1%) received EGFR-TKI monotherapy (no adjuvant chemotherapy). Patients who received adjuvant EGFR-TKIs had longer DFS than those who did not ($P = 0.033$) or those who received conventional adjuvant chemotherapy ($P = 0.038$). Adjuvant EGFR-TKIs did not alter OS ($P = 0.258$), although the recipients had better 3-year OS (92.5% vs. 81%). Eight patients who received adjuvant EGFR-TKI developed disease recurrence; 7 of these 8 patients developed recurrence during adjuvant treatment [31]. Again, this was a retrospective analysis so the patients who received EGFR TKI

Please cite this article in press as: J.C. Chuang, et al., Adjuvant therapy for EGFR mutant and ALK positive NSCLC: Current data and future prospects, Lung Cancer (2015), http://dx.doi.org/10.1016/j.lungcan.2015.07.016