Lung Cancer 84 (2014) 97–100

Contents lists available at ScienceDirect

Lung Cancer

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

Editorial

Molecular targeted therapy for early-stage non-small-cell lung cancer: Will it increase the cure rate?

ARTICLE INFO

Keywords:
Non-small cell lung cancer
Targeted therapies
Early-stage
Locally-advanced stage

ABSTRACT

Non-small-cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases, with a world-wide annual incidence of around 1.3 million. Surgery remains the corner stone of treatment in early-stage NSCLC when feasible, and the addition of adjuvant cisplatin-based chemotherapy has improved these results in resected NSCLC patients. For those patients with non-metastatic NSCLC not suitable for complete surgical resection, chemotherapy plus radiotherapy remains the best treatment option. For patients with metastatic NSCLC, molecular targeted agents have become part of the therapeutic arsenal in recent years. However, to date no targeted agent has been approved for patients with early or locally-advanced stages of NSCLC. Here, we review the rationale, literature and studies addressing the role of targeted agents used in the adjuvant setting or as part of chemoradiotherapy regimens.

1. Introduction

Non-small-cell lung cancer (NSCLC) represents approximately 85% of all lung cancer cases, with a world-wide annual incidence of around 1.3 million [1]. The therapy of choice for early-stage NSCLC is surgical resection, with 5-year survival rates from 73% for pathologic stage IA to 24% for stage IIIA [2].

In recent decades, a number of strategies have been studied with a view to improving outcome for patients with completely resected NSCLC. Adjuvant radiotherapy was not found to prolong survival and was even deleterious in patients with pathologic stage I–II NSCLC [3]. In 2004, the International Adjuvant Lung Cancer Trial (IALT) showed an absolute survival benefit of around 5% for adjuvant cisplatin-based chemotherapy [4]. As a result of toxicity, one fourth of the patients in this study received only one to two cycles of adjuvant cisplatin, and some 50% received less than the planned dose. There clearly remains room for more effective and better-tolerated adjuvant therapies.

For patients with metastatic NSCLC, molecular targeted agents have now been accepted therapeutic option. For example, bevacizumab has demonstrated efficacy when used in combination with chemotherapy in first-line setting in patients with non-squamous histology [5]. In addition, a number of molecular targeted therapies have demonstrated activity when used alone. Of particular interest are the inhibitors of the tyrosine kinase domain activity of the EGFR protein (EGFR-TKIs) for patients harboring mutations in the EGFR gene, and anaplastic lymphoma kinase (ALK) inhibitors for those patients with ALK translocations [6,7].

Despite the favorable results achieved with targeted agents in subgroups of NSCLC patients with metastatic disease, no targeted agents has yet been approved for use in patients with early or locally-advanced NSCLC.

2. EGFR–TKIs

The EGFR–TKIs erlotinib, gefitinib and afatinib represent therapeutic options in the treatment of metastatic NSCLC patients harboring EGFR mutations. Trials supporting the role of those three agents in first-line for EGFR-mutant patients [8–11] achieved superior results when compared to chemotherapy in terms of progression free survival (PFS), response rate, and quality of life. In addition, erlotinib can be used in patients with advanced NSCLC as maintenance or after failure of chemotherapy irrespective of EGFR status [12,13]. The potential benefit of EGFR–TKIs in combination with surgery or radiotherapy in patients with non-metastatic EGFR-mutant tumors has yet to be defined.

In the cancer and leukemia group B (CALGB) study 30106, sixty patients with unresectable stage III NSCLC received two cycles of induction paclitaxel/carboplatin and gefitinib [14]. Patients were divided in two strata according to performance status (PS) and weight loss; the poor risk stratum was defined as PS of 2 and/or ≥5% weight loss in previous 3 months while the good risk stratum was defined as PS 0–1 and <5% weight loss. Patients in the good risk stratum ($n = 39$) received weekly carboplatin plus paclitaxel with daily gefitinib all concurrent with thoracic radiotherapy up to 66 Gy. Those patients in the poor risk stratum ($n = 21$) received daily gefitinib with the same radiotherapy scheme. All patients received gefitinib maintenance until progression. Both treatment schedules were considered tolerable but results in terms of efficacy were disappointing. Poor risk patients had a median PFS of 13.4 months and an overall survival (OS) of 19.9 months. Good risk patients exhibited a worse outcome with a median PFS of 9.2 months and a median OS of 13 months. In forty-five patients EGFR and KRAS mutations were successfully analyzed. A total of 13 (29%) tumors had EGFR activating mutations and 7 (16%) had KRAS mutations; mutant patients were well balanced between the two strata. Although the interpretation of the results is inconclusive

0169-5002/$ – see front matter © 2014 Elsevier Ireland Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.lungcan.2014.01.018

because of the small sample size, there was no indication of differences among outcomes according to these two mutations.

The role of EGFR–TKIs in the treatment of stage III patients was also addressed in the SWOG S0023 [15]. In this study, patients with unresectable locally-advanced NSCLC (stage IIIA and IIIB) received cisplatin/etoposide with concurrent thoracic radiotherapy followed by consolidation docetaxel, all non-progressing patients were then randomized to either maintenance gefitinib or placebo. The trial was closed prematurely with 620 of the 840 patients expected following the preliminary negative results of the ISEL (Iressa Survival Evaluation in Lung Cancer) trial comparing gefitinib with placebo in previously-treated advanced NSCLC patients. In the SWOG 0023 study, gefitinib was associated with a significantly detrimental impact on OS ($p = 0.013$). This result seems to be related to a trend toward increased probability of disease recurrence as a cause of death in the gefitinib arm. The biological rationale for this result remains unclear.

A similar trial was conducted by Rigas and colleagues [16]. A total of 243 patients with unresectable stage III NSCLC were allocated to receive chemotherapy plus concurrent thoracic radiotherapy followed by docetaxel and then randomized to either maintenance erlotinib or placebo. This study demonstrated no significant difference in the primary end-point of PFS. The median PFS was 13.5 months *versus* 10.4 months for patients receiving placebo or erlotinib, respectively. Moreover, there was no differences in the median OS (30.4 months in the erlotinib arm *versus* 25.1 months in the placebo arm, p = non significant).

Results from these three studies suggest that no benefit is achieved by adding EGFR–TKIs to chemotherapy and thoracic radiotherapy in the treatment of unselected stage III NSCLC patients.

There are few data relating to patients with resected NSCLC harboring EGFR activating mutations and the potential efficacy of using adjuvant EGFR–TKIs. Jangijian and colleagues, reviewed outcomes of 167 patients with an exon 19 or 21 mutation treated at Memorial Sloan-Kettering Cancer Center with adjuvant erlotinib or gefitinib, either alone or with the use of adjuvant platinum-based chemotherapy[17]. The disease-free survival (DFS) at 2 years was 89% for patients receiving an EGFR inhibitor, compared with 72% for those who did not receive an EGFR–TKI (HR 0.53, $p = 0.06$). There was also a modest trend toward longer OS at 2 years in patients treated with an EGFR–TKI (96% *versus* 90%, HR 0.62, $p = 0.296$).

The results of the National Cancer Institute Canada (NCIC) CTG BR19 study analyzing adjuvant gefitinib have recently been published [18]. In this study, patients with completely resected (stage IB–IIIA) were randomized to gefitinib or placebo. Patients could have previously received adjuvant chemotherapy or radiotherapy. In April 2005, based on the negative results from the interim analysis of the SWOG S0023 study, the BR19 Data and Safety Monitoring Committee recommended study closure and discontinuation of study medication. A total of 503 patients were included and randomized 1:1 to gefitinib or placebo. The study failed to demonstrate the superiority of gefitinib over placebo. The median PFS was 4.2 years in the gefitinib arm and not reached in the placebo arm (HR 1.22; 95% CI, 0.93 to 1.61; $p = 0.15$). The median OS on gefitinib was 5.1 years and had not been reached for placebo patients (HR 1.24; CI 0.94 to 1.64; $p = 0.14$). Among the 503 patients included, EGFR mutation status was determined in 359 (71%). Only 15 (4%) had EGFR mutations. The presence of EGFR mutation was not a significant prognostic factor for DFS (HR 0.95; 95% CI, 0.30 to 3.01; $p = 0.93$) or OS (HR 0.57, 95% CI, 0.14 to 2.33; $p = 0.43$) but analyses were limited by the low mutation rate. KRAS mutation status was determined in 350 patients and its presence was not found to be a significant prognostic factor for either DFS or OS.

The French adjuvant therapy trial IFCT.0801 also addressed the role of adjuvant EGFR–TKIs in patients with EGFR mutations. In this trial, patients with resected stage II–IIIA non-squamous NSCLC were randomized to either standard adjuvant chemotherapy (cisplatin/pemetrexed) or to an experimental arm in which treatment was customized according to ERCC1 tumor expression and EGFR mutation status; patients with EGFR mutations were allocated to adjuvant erlotinib, while those with EGFR wild-type tumors were assigned to cisplatin/pemetrexed if they had low tumor ERCC1 expression or to observations alone in the case of high ERCC1 expression. However, the planned phase III study was cancelled after recruitment of 150 patients in the phase II due to new insights regarding the ERCC1 isoforms and the problems designing an accurate immunohistochemistry assay. No results on DFS or OS are available for the 150 patients included in the phase II part [19].

A further large trial from which we may learn more about the potential benefit EGFR–TKI therapy is the RADIANT trial. This trial included patients with completely resected stage IB-IIIA whose tumors expressed EGFR by immunohistochemistry and/or gene amplification by fluorescence in situ hybridization (FISH). These patients, who may have previously been treated with adjuvant chemotherapy, were randomized to receive either placebo or erlotinib for up to 2 years. Although the trial was not specifically designed to address the contribution of adjuvant erlotinib for patients with EGFR mutations, this subpopulation is expected to be retrospectively analyzed. The recruitment for this trial has now been completed.

In summary, at present, there is no evidence to support the use of EGFR–TKI as adjuvant treatment in resected NSCLC patients harboring EGFR mutations and in combination with chemotherapy and thoracic radiotherapy in stage III patients outside of a clinical trial.

3. EGFR monoclonal antibody therapy

For metastatic NSCLC, a phase III trial of cisplatin/vinorelbine alone or with cetuximab has demonstrated a statistically significant longer OS with the addition of cetuximab [20]. A number of studies have addressed the contribution of adding cetuximab to treatment of locally advanced NSCLC.

In the CALGB 30407 study patients with unresectable stage III NSCLC received four cycles of carboplatin/pemetrexed concurrently with thoracic radiotherapy with or without cetuximab and followed by four additional cycles of single agent pemetrexed. Although the trial was not designed to compare the efficacy of the two treatment arms, the failure-free survival (FFS) and OS outcomes were similar, with 22 months OS in both arms [21].

The radiation therapy oncology group (RTOG) trial 0324 was a single-arm, phase II trial that evaluated cetuximab plus weekly carboplatin/paclitaxel given concurrently with thoracic radiotherapy up to 63 Gy followed by cetuximab plus carboplatin/paclitaxel every 3 weeks for two cycles. The median OS was 22.7 months and grade 3 or higher pneumonitis and esophagitis were observed in only 7% and 8% of cases, respectively [22]. Prompted by these results the RTOG planned a phase III trial; in the RTOG 0617 study patients with unresectable stage III NSCLC were randomized to standard-dose or high-dose radiotherapy (60 Gy *versus* 74 Gy) combined with concurrent carboplatin/paclitaxel alone or with cetuximab. In the study, 60 Gy was found to be superior to 74 Gy in terms of OS (28.7 *versus* 19.5 months, $p = 0.0007$) and local failure rates at 18 months (25.1% *versus* 34.3%, $p = 0.03$) [23]. The effect of cetuximab has also been recently presented [24]. Non-hematologic toxicity ≥grade 3 was higher in the cetuximab group, 70.5% *versus* 50.7% ($p < .0001$). Median OS was 23.1 *versus* 23.5 months, 18-month OS rates were 60.8% *versus* 60.2% in the cetuximab arm *versus* non-cetuximab arm, respectively ($p = 0.484$, HR = 0.99).

Results from the CALGB 30407 and RTOG 0324 studies suggest that further evaluation of cetuximab in the treatment of stage III NSCLC in combination with chemotherapy and thoracic radiotherapy is unlikely to provide benefit in an unselected population.