How to integrate current knowledge in selecting patients for first line in NSCLC?

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Non-small-cell lung cancer (NSCLC) accounts for 80% of all lung cancer, which is the leading cause of cancer mortality. The majority of NSCLC patients present with advanced disease at diagnosis. Standard chemotherapy using platinum-containing doublets has reached a therapeutic plateau with a median survival of ~1 year. The development of more effective strategies in the first-line setting remains challenging. In selected chemotherapy-naïve, advanced, non-squamous patients, the combination of bevacizumab with chemotherapy was shown to produce better outcomes than chemotherapy alone. The potential benefit of maintenance/sequential treatment after initial platinum-based chemotherapy should be discussed in detail with each patient. Epidermal growth factor receptor (EGFR) mutation determination should be carried out in subgroups of patients characterized by a high prevalence of sensitizing mutations. When a mutation is present, first-line treatment with an EGFR tyrosine kinase inhibitor may be considered. Finally, a phase I study using an oral ALK inhibitor has produced promising results in NSCLC patients with ALK rearrangements, indicating that ALK represents a new therapeutic target in a molecularly defined subset of NSCLC. Ongoing studies in first-line therapy are focusing on targeted therapies and patient selection.

Key words: first-line treatment, molecular analyses, NSCLC, targeted therapies

introduction

Non-small-cell lung cancer (NSCLC) represents ~80% of all cases of lung cancer, which is the leading cause of cancer mortality worldwide. The outcome for patients with advanced NSCLC remains poor with median survival times approaching 12 months [1, 2].

The standard therapy for patients with advanced-stage disease is platinum-based double-agent chemotherapy with equal efficacy being observed with several combinations [3, 4]. Recent evidence indicates that histology represents a relevant variable in the decision-making process [4, 5]. In the Scagliotti et al. [4] study comparing cisplatin with either gemcitabine or pemetrexed in the first-line setting, the authors showed higher efficacy for the pemetrexed combination, when compared with cisplatin/gemcitabine, in those patients with non-squamous histology. This effect could be explained by the activity of thymidylate synthase, an enzyme overexpressed in squamous cell carcinoma and involved in folic acid metabolism [5]. Thus, in this study, histology is probably acting as a surrogate for molecular markers. Strategies developed to improve the chemotherapy benefit are actually evaluating a maintenance/sequential therapy with the continuation or the early administration of a different chemotherapeutic agent. The essential prerequisites for maintenance/sequential therapy include good drug tolerability, and an in increase in overall survival (OS). In patients with stage III or IV disease who had not progressed following four cycles of platinum-doublet chemotherapy, sequential pemetrexed obtained a significant improvement in progression-free survival (PFS) (4.3 months compared with 2.6 months, \( P < 0.001 \)) and OS (13.4 months compared with 10.6 months, \( P = 0.012 \)) when compared with placebo [6]. The SATURN study evaluated sequential therapy with erlotinib in patients with no evidence of progression after four cycles of standard first-line platinum-based chemotherapy and showed a statistically significant improvement in PFS and OS in those patients who received erlotinib treatment [7].

anti-angiogenic therapies

Bevacizumab is a humanized monoclonal antibody directed against the vascular endothelial growth factor (VEGF). In chemotherapy-naïve patients with advanced, non-squamous cell carcinoma tumors, the combination of bevacizumab with chemotherapy has been shown to produce better outcomes than chemotherapy alone in two randomized trials. In the ECOG 4599 trial the addition of bevacizumab to a paclitaxel/carboplatin combination produced a benefit in OS when compared with chemotherapy alone (12.3 versus 10.3 months, \( P = 0.003 \)) [8]. In the AVAIL trial, patients with advanced non-squamous cell carcinoma were randomized to receive either cisplatin/gemcitabine or the same combination with bevacizumab at two different doses. In this study, the combination of bevacizumab with cisplatin/gemcitabine significantly improved PFS [9], the primary endpoint; although there were no differences in OS [10]. Recent data from the
ECOG 4599 trial has indicated that the onset of high blood pressure during treatment with paclitaxel/carboplatin/bevacizumab may be associated with improved outcomes.

Sorafenib is an oral small-molecule tyrosine kinase inhibitor, targeting Raf kinases, VEGF receptor (VEGFR), platelet-derived growth factor receptor (PDGFR) and c-kit. A recent phase III study assessed the efficacy and safety of sorafenib in combination with carboplatin/paclitaxel in chemotherapy-naive patients with advanced NSCLC [11]. On the basis of a planned interim analysis, OS was 10.7 months in the sorafenib arm and 10.6 months in the placebo arm. The study was terminated after the interim analysis concluded that the study was highly unlikely to meet its primary endpoint of improving survival. A prespecified exploratory analysis revealed greater mortality in patients with squamous cell carcinoma histology in the sorafenib arm compared with those in the placebo arm.

Sunitinib is an oral multitarget tyrosine kinase inhibitor that inhibits VEGFR, PDGFR and c-kit. In a recent phase I study, the combination of gemcitabine/cisplatin/sunitinib administered to chemotherapy-naive patients achieved promising evidence of antitumor activity, although frequent dose delays due to myelosuppression occurred [12].

Vandetanib, an oral inhibitor of the VEGFR and epidermal growth factor receptor (EGFR) signalling pathways was analyzed in the first-line setting in a randomized phase II trial comparing paclitaxel/carboplatin against vandetanib alone against carboplatin/paclitaxel/vandetanib. Compared with the paclitaxel/carboplatin arm, patients receiving paclitaxel/carboplatin/vandetanib had longer PFS, whereas those receiving vandetanib monotherapy had shorter PFS [13].

**EGFR inhibitors**

EGFR is a member of the human epidermal receptor family overexpressed in 50%–80% of NSCLC patients with a stimulatory effect on cell proliferation, survival, migration and angiogenesis. There are two principal strategies designed to inhibit the EGFR pathway: monoclonal antibodies and tyrosine kinase inhibitors.

Cetuximab is a chimeric immunoglobulin G1 monoclonal antibody that binds to the extracellular domain of the EGFR. Previous phase II trials in the first line demonstrated improvement in response rate and OS with the addition of cetuximab to chemotherapy [14, 15]. Two randomized phase III trials comparing platinum-based therapy with or without cetuximab have been reported. In the FLEX trial, 1125 patients with EGFR-positive tumors by immunohistochemistry were randomized to receive cisplatin/vinorelbine with or without cetuximab [16]. This trial met its primary endpoint with an increase in OS in the cetuximab arm (11.3 compared with 10.3 months, \( P = 0.044 \)). In the BMS 099 trial, 676 chemotherapy-naive patients with advanced disease were randomized to receive carboplatin/taxane combination or carboplatin/taxane/cetuximab [17]. The addition of cetuximab to paclitaxel/carboplatin did not significantly improve PFS. There was a non-significant trend toward better OS in the cetuximab arm (9.7 months compared with 8.4 months, \( P = 0.17 \)). Recent analyses in these two trials assessing potential biomarkers predictive of outcomes, EGFR expression by immunohistochemistry, FISH or EGFR mutation was not found to correlate with results in the cetuximab arm [18, 19].

Gefitinib and erlotinib, the most studied EGFR tyrosine kinase inhibitors, have been extensively evaluated in combination with standard chemotherapy regimens in chemotherapy-naive patients with advanced NSCLC with no benefit in the response rate, PFS or OS [20–23]. One possible explanation is that EGFR tyrosine kinase inhibitors induce cell cycle arrest in the G1 phase, which makes the cells less sensitive to cytotoxic agents.

There is, at present, clear evidence to indicate that in patients with advanced NSCLC, activating mutations in the EGFR gene confer hypersensitivity to the tyrosine kinase inhibitors, gefitinib and erlotinib. Almost 90% of lung-cancer-specific EGFR mutations comprise a leucine-to-arginine substitution at position 858 (L858R) and deletion mutants in exon 19 that affect the conserved sequence LREA (delE746–A750). These mutations cause constitutive activation of the EGFR tyrosine kinase domain by destabilizing its auto-inhibited conformation, which is normally maintained in the absence of ligand stimulation. Several studies have shown that EGFR mutations are independent predictors of response and PFS in patients treated with EGFR tyrosine kinase inhibitors. In all these studies, EGFR mutations were found to be more frequent in women, patients with adenocarcinomas, never-smokers and East Asians.

In the IPASS phase III study, 1217 Asian, never-smoker, chemotherapy-naive patients with advanced adenocarcinoma were randomly assigned to receive gefitinib or paclitaxel/carboplatin [24]. The study met its primary objective of showing the non-inferiority of gefitinib and also showed its superiority, as compared with carboplatin/paclitaxel with respect to PFS. In the subgroup of 261 patients who were positive for the EGFR mutation, PFS was significantly longer among those who received gefitinib than among those who received carboplatin/paclitaxel [hazard ratio (HR) 0.48; \( P < 0.001 \)]. However, in the subgroup of patients who were negative for the mutation, PFS was significantly longer among those who received chemotheraphy (HR 2.85; \( P < 0.001 \)).

The West Japan Oncology Group conducted a phase III trial in which EGFR-mutated patients were randomized to receive chemotherapy with either cisplatin/docetaxel or gefitinib [25]. In this trial patients with EGFR mutation had longer PFS if they were treated with gefitinib than if they received cisplatin/docetaxel (9.2 compared with 6.3 months, \( P < 0.0001 \)). More mature data of OS are awaited.

In another phase III study in Japanese patients harbouring EGFR mutation, patients were randomized to receive first-line treatment with gefitinib versus chemotherapy with carboplatin/paclitaxel. After 200 patients were included, a pre-planned analysis showed that PFS significantly improved with gefitinib (10.4 compared with 5.5 months) [26].

In Spain, lung cancer samples from 2105 patients from 129 institutions were prospectively screened for EGFR mutations, from April 2005 through November 2008; patients with EGFR mutations were eligible for erlotinib treatment. EGFR mutations were found in 350 of the 2105 patients (16.6%) [27]. Mutations were more frequently found in
women, in never-smokers and in those with adenocarcinoma. The mutations observed were deletion in exon 19 in 62.2% of the patients and L858R in 37.8%. Median PFS for EGFR-mutated patients receiving erlotinib as second-line therapy was 13.0 months, with an OS of 28.0 months; an improvement over previously reported findings in lung cancer patients. These results highlight the idea that EGFR-mutant lung cancer is a different type of NSCLC. At present, the most favorable sequence of these agents (in first-line or second-line treatment) has yet to be established. The results of a prospective study of the Spanish Lung Cancer Group with erlotinib versus chemotherapy in EGFR-mutated patients in first line is awaited to confirm the IPASS trial results in a non-Asian population (EURTAC trial).

investigational strategies in first-line treatment

Anaplastic lymphoma kinase (ALK) rearrangements represent one of the newest molecular targets in NSCLC. At present, ALK rearrangement defines a molecular subset of NSCLC with distinct clinical characteristics. Shaw et al. [28] studied the prevalence of ALK rearrangements in selected patients according to clinical characteristics such as female sex, Asian ethnicity, little or never smoking history and adenocarcinoma histology. ALK rearrangements were present in 13% of the tumours screened and were mutually exclusive with EGFR mutation. Compared with the EGFR mutant cohort, patients with ALK rearrangements were significantly younger and were more likely to be men. In this study, ALK rearrangements were associated with resistance to EGFR tyrosine kinase inhibitors. A recent phase I trial study with an oral ALK and MET inhibitor (PF-02341066) in previously treated patients, reported a disease control rate at 8 weeks of 70% [29].

In NSCLC, in addition to EGFR mutation and ALK rearrangements, other mutations have been identified, including BRAF and HER2. PIK3CA mutations or copy number gains have been detected in ~5% of NSCLC tumors samples. Genomic amplification of the MET gene is seen in ~3% of NSCLCs. Such findings highlight the potential relevance of identifying genomic alterations in tumor samples. There is an increasing body of evidence that the clinical benefit associated with targeted therapies is limited to a subset of patients [30]. The development of effective strategies to implement personalized medicine will soon include tumor genotyping in samples from patients with NSCLC; this may well change first-line treatment in subgroups of NSCLC patients in the near future.

disclosures

The authors have declared no conflict of interest.

references