Clin Oncol Cancer Res (2011) 8: 220–223
DOI 10.1007/s11805-011-0584-6

Multi-Targeted Therapies in Non-Small Cell Lung Cancer

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Recieved May 18, 2011; accepted August 20, 2011

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ABSTRACT Current treatment modalities provide limited improvement in the natural course of lung cancer, and prognosis remains poor. Lung cancer is a malignancy with great molecular heterogeneity. The complexity of the signaling process leading to cancer cell proliferation and to the neoplastic phenotype supports the necessity of interfering at different stages to avoid cancer cell resistance to therapy. For this reason, new strategies for the simultaneous inhibition of multiple molecular targets are being pursued.

KEY WORDS: multi-targeted therapies, non-small cell lung cancer, tyrosine kinase inhibitors, vascular endothelial growth factor receptor.

Introduction

Lung cancer is the leading cause of cancer death world-wide[1]. and in Asia the mortality rate has increased rapidly. A total of 1.2 million cancer deaths worldwide were from lung cancer in 2002[2]. Non-small cell lung cancer (NSCLC) accounts for about 80% of all lung cancers. Conventional treatment of NSCLC has apparently reached a plateau of effectiveness in improving survival, and treatment outcomes must still be considered disappointing[3]. Current treatment modalities, including chemotherapy, radiotherapy and surgery, have provided only limited improvement in the natural course of this disease. Therefore, the development of new therapeutic strategies is highly awaited[4]Major progress in understanding of the cancer biology and mechanisms of oncogenesis has allowed the development of several potential molecular targets for NSCLC treatment. Approximately 85% of lung cancers are of non-small cell-type (NSCLC), a form comprised of diverse histological subtypes originating in lung epithelial cells[4]. These targets are components of signaling pathways or metabolic processes contributing to the acquisition of cancer phenotype. Several targeted agents have been introduced in clinical trials in NSCLC and a series of phase III studies has already produced definitive results. The main agents that have been investigated are epidermal growth factor receptor (EGFR), tyrosine kinase family inhibitors (TKIs), angiogenesis inhibitors, and various signal transduction inhibitors. VEGF also increases vascular permeability, contributing to malignant pleural effusion in NSCLC[5,6]. EGFR–TKIs, such as gefitinib and erlotinib, are active as single agents in a subset of patients with specific anatomopathologic and biologic features[7–10].

The combination of different specific molecular target inhibitors is especially appealing since such an approach may theoretically improve

clinical efficacy with minimal cumulative toxicity. Agents targeting multiple pathways in tumor growth are also highly attractive, potentially offering the benefits of combined therapy within a single agent. The majority of these newer agents inhibits more than one receptor tyrosine kinase and may have unique inhibition profiles[10].

Multitargeted therapies

The FDA approval of bevacizumab (Avastin), a humanized VEGF-targeting monoclonal antibody, for the first-line treatment of advanced or metastatic non-squamous cell NSCLC was based on results from a randomized, openlabel phase 3 trial (ECOG 4599) that showed that the addition of 15 mg/kg bevacizumab (BV) to carboplatin/paclitaxel (CP) reduced the risk of death by 20% *vs.* CP alone (HR, 0.79)[11]. Along with the combination of EGFR inhibitors with agents selectively targeting one signalling protein, the use of drugs with multitargeting capability against several kinase receptors and intracellular targets has been proposed. Several clinical trials of combination therapies with multitargeted agents are currently ongoing. In fact, compounds as ZD6474 (ZactimaTM), SU11248(SunitinibTM) and BAY 43–9006 (SorafenibTM), multi-tyrosine kinase inhibitors, are under clinical evaluation in NSCLC.

ZD6474

ZD6474 selectively targets two key pathways in tumour growth by inhibiting vascular endothelial growth factor (VEGF)-dependent tumour angiogenesis and epidermal growth factor (EGF)-dependent tumour cell proliferation and survival. ZD6474 is a novel oral heteroaromatic-substituted anilinoquinazoline that acts as a potent and reversible inhibitor of ATP binding to VEGFR-2 (Vascular Endothelial Growth Factor Receptor-2 or KDR) and to EGFR (Epidermal Growth Factor Receptor) tyrosine kinase. By targeting these two pathways, ZD6474 may therefore provide greater benefit than blockade of either pathway alone. RET kinase has also been identified as a third target for ZD6474[12].

Two phase I studies were conducted in USA, Australia and in Japan, which demonstrated a maximum tolerated dose of 300 mg, with common adverse events being diarrhoea, rash and asymptomatic QTc prolongation. In the Japanese study with doses ranging from 100 mg to 400 mg, objective tumour response was seen from 4 of 9 patients with NSCLC[13].

Phase II trials of ZD6474 at doses of 100 mg or 300 mg are ongoing in a range of tumours types in single and combination regimens. These include three randomised studies of patients with advanced NSCLC. In order to determine the additional benefit of VEGFR tyrosine kinase inhibition, a comparative study of ZD6474 and gefitinib has been initiated in previously treated patients with stage IIIB-IV NSCLC. The crossover design also allows assessment of the activity of ZD6474 in subjects who have failed treatment with gefitinib. In part A, patients have received daily oral doses of either ZD6474 300 mg or gefitinib 250 mg, until withdrawal due to disease progression, toxicity or removal of informed consent. After a washout period of 4 weeks, patients have been switched to the alternative treatment (part B), continued until a withdrawal criterion was reached. The initial phase A of this study is now complete and the preliminary results evidenced a significant improvement in progression-free survival (PFS) with ZD6474 therapy compared with gefitinib (11.9 weeks for ZD6474 *vs.* 8.1 weeks for gefitinib; HR = 0.63, 95% CI: 0.44–0.90; P = 0.011)[14].

In the other two trials with the same design (an open-label safety run-in phase followed by a randomized placebo controlled phase), the efficacy of ZD6474 in combination with standard chemotherapy regimens is being compared with that of standard chemotherapy alone: one ongoing with carboplatin-paclitaxel in first-line treatment[15] and the second completed with docetaxel in patients who progressed after platinum containing therapy[16].

In first-line, the run-in phase of this study has demonstrated that the combination of ZD6474 and carboplatin-paclitaxel was generally well tolerated without mutually additive toxicity. Partial responses have been observed in seven out of 18 patients and stable disease 12 weeks in a further two patients. These preliminary results have supported progression to the randomised phase, which is currently ongoing[17].

In second-line treatment, ZD6474 at 100 mg or 300 mg, in combination with docetaxel, showed prolonged PFS respect docetaxel alone. In this trial a total of 127 patients were randomized and the estimated HRs for PFS were 0.64 (95% CI: 0.38–1.05; P = 0.074) for ZD6474 100 mg + docetaxel and 0.83 (95% CI: 0.50–1.36; P = 0.416) for ZD6474 300 mg + docetaxel. The estimated median PFSs were 18.7, 17 and 12 weeks for ZD6474 100 mg, 300 mg and for docetaxel alone, respectively. Objective responses were observed in 26, 18 and 12% of patients in treatment with ZD6474 100 mg, 300 mg and with docetaxel alone, respectively, with rates of disease control for at least 6 weeks of 83, 64 and 56%, respectively[18].

These studies in a broad population of patients with advanced NSCLC show that ZD6474 is well tolerated alone and in combination with chemotherapy, with promising data in the treatment of recurrent disease. The development of this agent in other stages of NSCLC (planned EORTC phase II trial: radiotherapy *vs.* radiotherapy followed by ZD6474 *vs.* radiotherapy concomitant with ZD6474 in patients with NSCLC stage III after 2 cycles of platinum-based chemotherapy as induction) and in phase III has been initiated.

Sorafenib

Sorafenib (Nexavar Bayer, Leverkusen, Germany) is a novel potent oral kinase inhibitor of Raf-1 and also active against VEGFR 2, VEGFR 3, platelet-derived growth factor b (PDGFR b), and c-KIT[32]. Thus, sorafenib has the potential to prevent tumor cell proliferation and

angiogenesis by blocking the Raf/MEK/ERK pathway at the level of Raf kinase and receptor tyrosine kinases VEGFR 2 and PDGFR b. Sorafenib has shown significant dose-dependent antitumor activity in several preclinical models of different human tumor types that express a mutation in K-Ras or B-Raf, including A549 NSCLC xenograft models[19]. Thirty-one Japanese patients, including 10 with NSCLC, were enrolled in a recent phase I trial[20] to establish the recommended dose for phase II trials and to determine toxicity profile and pharmacokinetics. The most common adverse events were skin toxicities, diarrhea, and anorexia. One patient with NSCLC treated at the 200-mg twice-daily dosage reported a partial response, while two other patients with NSCLC had stable disease for 24 weeks or more, at a 200 or 400-mg twice-daily dosage. On the basis of those data, the recommended dosage of sorafenib for phase II trials is 400mg twice daily. Since preclinical data in the A549 NSCLC xenograft model showed that sorafenib did not antagonize the effect of the EGFR-TKI gefitinib, a phase I trial of the combination of gefitinib and sorafenib[16] was conducted in 12 patients with refractory or recurrent NSCLC. Serious drug-correlated adverse events were seen in three patients and consisted of diarrhea and dyspnea. The results were one partial response and eight patients with stable disease. The dosages recommended for phase II trials were 400mg twice daily for sorafenib and 250 mg once daily for gefitinib. Vandetanib (ZD6474), a once-daily oral TKI, is the most clinically mature for NSCLC. Results from several phase 2 studies in different NSCLC treatment settings have produced encouraging results, and four randomized phase 3 trials of vandetanib have been initiated in refractory NSCLC: vandetanib *vs.* placebo; *vs.* erlotinib; ±docetaxel; and ± pemetrexed. Therapies directed at other angiogenic targets, such as the insulin-like growth factor receptor-1 (IGFR-1) and mammalian target of rapamycin (mTOR), part of the PI3/Akt pathway, are also being investigated for advanced NSCLC.

Sunitinib

Sunitinib is a novel oral multitargeted TKI with activity against VEGFR 1, VEGFR2, VEGFR 3, c-KIT, PDGFR a, and PDGFR b, having both antitumor and antiangiogenic activities. In xenograft models (including the NSCLC cell line H460 and the SCLC cell line NCI-H526), sunitinib exhibited a potent antitumor activity[21,22]. Sunitinib is under clinical evaluation in NSCLC and SCLC in second-line treatment, both as a single agent and in combination with erlotinib. Sunitinib (Sutent) 50 mg/kg/day (4 weeks on, 2 weeks off) was evaluated in a single-arm phase 2 study of 63 treatment-refractory NSCLC patients12. Median PFS and OS were 2.8 mo. and 6 mo., respectively, with an objective response rate of 11.1%. In a subsequent phase II trial, a median PFS and OS of 3.1 mo. And 9.3 mo. were reported using continuous dosing of sunitinib 37.5 mg/day in 47 treatment-refractory NSCLC patients[23]. Sunitinib has been associated with both pulmonary and cerebral hemorrhage in NSCLC patients[24]. Additionally, patients receiving sunitinib may require monitoring for development of hypothyroidism, reduced left ventricular ejection fraction (LVEF), and QT interval prolongation[25,26].

Several small-molecule vascular endothelial growth factor receptor tyrosine kinase inhibitors have also shown promise in phase I and II trials in NSCLC. This review summarizes the most important findings on angiogenesis inhibitors in NSCLC and discusses the potential for the use of these novel agents in different settings.

Conclusion

The use of targeted therapies, particularly those against the key mediator of angiogenesis, vascular endothelial growth factor, has the potential to improve outcomes for nonsmall cell lung cancer (NSCLC) patients. This review summarizes recent findings on targeting mediators of angiogenesis, treatment options and molecular targets in development.

Preclinical and clinical data suggest that targeting multiple pathways in tumor cells should be an effective strategy of treatment in NSCLC, New agents targeting multiple receptor tyrosine kinases are especially appealing due to their ability of blocking several pathways thereby overcoming possible resistance to more selective targeted agents. in consideration of a multilevel cross-stimulation among the molecular targets involved in tumor-genesis. Nevertheless, the clinical experience in this field is still limited. NSCLC may encourage other similar clinical studies evaluating the activity of multi-targeted agents. A series of important clinical issues should be addressed in ongoing and future clinical trials about EGFR–TKI and VEGF.

The use of biomarkers for identifying NSCLC patients most likely to respond to antiangiogenic therapies remains an active area of research, but requires validation. From a therapeutic standpoint, vascular disrupting agents (VDAs) represent a novel antivascular approach to NSCLC. VDAs selectively target existing tumor vasculature, resulting in rapid tumor necrosis. In a single-arm phase 2 study in chemo-naïve patients with advanced NSCLC, 11 of 30 who received the VDA DMXAA (ASA404) plus CP achieved a PR and 14 had SD; median survival was 14.9 months[26]. A second VDA, MPC-6827 (Azixa) is being evaluated in a phase 2 trial in NSCLC patients with BM. With numerous agents/combinations under investigation for NSCLC, clinicians should consider referring appropriate patients for participation in clinical trials, which provide the best opportunity to take advantage of evolving therapies and strategies.

Conflict of Interest Statement

No potential conflicts of interest were disclosed.

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