Multi-target inhibitors in non-small cell lung cancer (NSCLC)

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Lung cancer is the leading cause of cancer death world-wide [1]. 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 [2]. In the last years, there has been an explosion in the knowledge of the genetic and biologic understanding of lung cancer providing us with many novel potential targets for the development of different molecular targeted therapies. At least two of these novel agents, erlotinib and bevacizumab, have been proven to prolong survival in large randomized trials and serve as a ‘proof of the concept’ for the role of this new category of drugs in the treatment of advanced NSCLC [3, 4]. Nevertheless, it appears that the greatest benefit obtained with these compounds, in particular with EGFR (Epidermal Growth Factor Receptor) tyrosine kinase inhibitors, is confined to a tiny patient subgroup with specific biological features indicating the EGFR pathway as the predominant driving force for cell survival and proliferation of that specific tumour [5]. The discovery of activating EGFR mutations in the tyrosine kinase domain which increase sensitivity to EGFR tyrosine kinase inhibitors has opened a new avenue to patient selection for molecular targeted therapies [6]. However, most smoke-related bronchogenic neoplasms possess multiple molecular alterations and resistance to selective molecular-targeted agents can be explained, at least in part, by the presence of alternative pathways of cell proliferation signalling.

For this reason, new strategies for the simultaneous inhibition of multiple molecular targets are being pursued. One of these entails the combination of different molecular targets inhibitors. Alternatively, small molecules inhibiting multiple targets are under investigation. The combination of different specific molecular target inhibitors is especially appealing since such an approach may theoretically improve clinical efficacy with minimal cumulative toxicity. This is the basis, for example, for the combination of bevacizumab and erlotinib, which demonstrated encouraging results in a phase I/II study on 40 patients with pre-treated non-squamous stage IIIB-IV NSCLC [7]. Agents targeting multiple pathways in tumour 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 [8]. Particularly, this approach has been subject of considerable research in the field of lung cancer. In fact, compounds as ZD6474 (Zactima™), SU11248 (Sunitinib™) and BAY 43–9006 (Sorafenib™), multi-tyrosine kinase inhibitors, are under clinical evaluation in NSCLC.

ZD6474 (Zactima™)

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 [9].

This molecule inhibits the EGFR tyrosine kinase, though at an inhibitory concentration (IC50) of 500 nM, which was higher than that for VEGFR-2 (IC50 = 40 nM) (Table 1) [10]. ZD6474 has demonstrated to enhance the efficacy of radiation and certain cytotoxic chemotherapy, as paclitaxel [9, 11]. Once-daily oral dosing with ZD6474 has shown excellent reversible inhibition of tumour cell growth in a broad range of pre-clinical models, including lung cancer xenografts [10]. ZD6474 also displayed anti-tumour activity in a xenografts model with resistance to EGFR inhibitors (C225 and gefitinib), suggesting that this agent may be an effective treatment against tumours with acquired or intrinsic EGFR resistance, for its ability to inhibit VEGF signalling [9, 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 regimen. These include three randomised studies of patients with advanced NSCLC. In order to determine the additional benefit of VEGF 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...
Table 1. In vitro activity of ZD6474 (Zactima™), SU11248 (Sunitinib™) and BAY 43–9006 (Sorafenib™) against kinase targets

<table>
<thead>
<tr>
<th>Kinase</th>
<th>ZD6474 IC₅₀ (nM)</th>
<th>SU11248 IC₅₀ (nM)</th>
<th>BAY 43–9006 IC₅₀ (nM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>VEGFR-2 (KDR)</td>
<td>40</td>
<td>10</td>
<td>90</td>
</tr>
<tr>
<td>RAF</td>
<td>–</td>
<td>–</td>
<td>22</td>
</tr>
<tr>
<td>PDGFR-β</td>
<td>&gt;10.000</td>
<td>10</td>
<td>57</td>
</tr>
<tr>
<td>c-KIT</td>
<td>&gt;20.000</td>
<td>10</td>
<td>68</td>
</tr>
<tr>
<td>FLT-3</td>
<td>–</td>
<td>250</td>
<td>58</td>
</tr>
<tr>
<td>EGFR</td>
<td>500</td>
<td>–</td>
<td>–</td>
</tr>
</tbody>
</table>

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 [15].

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 [16].

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.

**SU11248 (Sunitinib™)**

SU11248 is a novel oral multi-targeted tyrosine kinase inhibitor with anti-tumour and anti-angiogenic activities. Sunitinib™ has been identified as a potent inhibitor of VEGFR-1, VEGFR-2, fetal liver tyrosine kinase receptor 3 (FLT3), c-KIT (stem-cell factor [SCF] receptor), PDGFR (Platelets-Derivated Growth Factor) -α and -β in both biochemical and cellular assays (Table 1). In mouse xenografts models, SU11248 exhibited broad and potent anti-tumour activity causing regression, growth-arrest or substantially reduced growth of various human cell lines, including of NSCLC (H460) and SCLC (NCI-H526) [17, 18]. Administered orally at 50 mg per day for 4 weeks every 6 weeks, this agent seems to be well tolerated, with the main adverse effects represented by sore mouth, oedema, asthenia, skin toxicity hypertension and mild myelo-suppression [19]. It has shown interesting activity in advanced renal cancer and in GIST resistant to imatinib. If for these types of tumour it is in advanced experimentation, SU11248 is also under clinical evaluation in lung cancer (NSCLC and SCLC) in second line treatment, both as single agent and in combination with erlotinib.

**BAY 43–9006 (Sorafenib™)**

BAY 43–9006 is a novel oral kinase inhibitor targeting RAF kinase. This agent has been shown in preclinical models to have activity against other several kinases, including VEGFR-2, PDGFR-β, c-KIT and FLT3 (Table 1). Thus, it has the potential to prevent tumour growth by combining two anticancer activities: inhibition of both tumour cell proliferation and tumour angiogenesis. BAY 43–9006 has shown significant dose-dependent anti-tumour activity in preclinical models of different human tumour types, including NSCLC [20]. It is well tolerated in adults at 400 mg bid; drugs-related adverse events were mainly mild-to-moderate and included hand-foot skin reaction, diarrhoea, fatigue, hypertension, pain and rash [21, 22]. Since preclinical data in the A549 NSCLC xenograft model show that BAY 43–9006 does not antagonize the effect of gefitinib, a phase I study of this combination was conducted [23]. This trial has shown that the recommended dose for the combination of Sorafenib™ and gefitinib is 400 mg/bid and 250 mg/die, respectively. This combination was well tolerated and demonstrated anti-tumour activity, primarily through disease stabilisation effects in 63% of patients. The potential activity of BAY 43–9006 in patients with advanced NSCLC is being evaluated in ongoing phase II–III trials, as single agent or in combination with gefitinib or chemotherapy.

**conclusions**

Preliminary preclinical and clinical data suggest that targeting multiple pathways in tumour cells might be an effective anti-tumour treatment strategy 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.

Nevertheless, the clinical experience in this field is still limited. More research is needed to assess whether efficacy of this new generation of tyrosine kinase inhibitors is superior to that of old generation ones and whether their activity is related or not to the expression of their specific targets.

references