Combination of biological therapies in non-small cell lung cancer

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Growth factor receptors control critical functions for human cancer cells, such as growth, angiogenesis, metastatic spread, inhibition of cell death and apoptosis via sequential signalling activation of several kinases involved in transduction pathways. Among those receptors, the epidermal growth factor receptor (EGFR) and its ligands EGF and TGFα have been extensively investigated for their crucial role in the pathogenesis of non small cell lung cancer (NSCLC). The results of a large body of preclinical studies and clinical trials suggest that targeting the EGFR could provide a contribution to cancer therapy. Among a variety of approaches used to target EGFR signaling, EGFR blocking monoclonal antibodies (mAbs) and small molecules inhibiting the EGFR tyrosine kinase (TKI) have been successfully developed in different types of human malignancies. Both types of agent exert a significant antiproliferative activity when used alone or in combination with conventional antitumor treatments, such as chemotherapy or radiotherapy. Although the advanced clinical development of EGFR blocking drugs demonstrates their efficacy in certain metastatic diseases, the role of these agents in NSCLC is still under investigation, due to discouraging and conflicting results of some clinical trials. The initial development of two quinazoline EGFR-TKI, such as gefitinib and erlotinib, for the treatment of advanced chemo-refractory NSCLC, demonstrated a good safety, objective responses and prolonged remissions in a minority of patients (9–20%) and substantial improvements in quality of life [1, 2]. However, the combination of these drugs with conventional chemotherapy for the treatment in first line of chemo-naive metastatic NSCLC failed to demonstrate a clear advantage over chemotherapy alone in terms of overall survival in four large randomized trials. The negative results of these combination trials have brought disappointment regarding the potential value of EGFR and its TKI in the treatment of NSCLC and pointed out the need of new therapeutic approach in clinical management of this disease. In this respect, several efforts have been made to identify crucial signal transduction effectors cooperating with EGFR in cancer cells, able to use multiple and redundant intracellular pathways to overcome blockade of a particular receptor or protein signal. Moreover, the potential for acquired resistance to growth factor signalling inhibition through EGFR alone suggests that attacking other pathways that contribute to cancer cell survival and angiogenesis, might further improve tumor control. Different types of biological inhibitors have been used to overcome constitutive or acquired resistance to TKI against EGFR: for example, treatment of gefitinib-resistant NSCLC cell lines, showing EGFR-independent activity of the PI3K/Akt or Ras/Erk pathways, with specific inhibitors of mTOR, PI3K, Ras or MEK antagonists, restores sensitivity to gefitinib [3]. Moreover, targeting multiple receptors members of the EGFR family could elicit an antiproliferative effect more powerful than single receptor inhibition. Combination of the EGFR TKI erlotinib, approved for clinical use in metastatic chemorefractory NSCLC, with pertuzumab, a novel humanized mAb that prevents heterodimerization of HER2 with other HER receptors, is able to induce a stronger antitumor activity in human NSCLC tumor xenografts, regardless of receptors expression, in comparison with single-agent therapy [4].

Tumor-induced angiogenesis is well known as a key player in sustaining local tumor growth, invasion and metastatic spread. Activation of EGFR signaling by EGF or by TGFα can up-regulate the production of VEGF in human cancer cells [5, 6] and several experimental evidences have demonstrated that EGFR blockade causes inhibition of the secretion of VEGF and of other angiogenic growth factors, including bFGF, interleukin 8, and TGFα [7, 8]. The increasing understanding of the molecular mechanisms that control angiogenesis has allowed the development of drugs that interfere with this process. Among the approaches that have been proposed for blocking VEGF-induced endothelial cell proliferation and subsequent tumor angiogenesis, neutralizing anti-VEGF mAbs, blocking mAbs against the VEGFR-2 or selective inhibitors of the VEGFR-2 TK, are currently in preclinical and clinical development [9, 10]. One of the most promising antiangiogenic agents in clinical development is bevacizumab, a humanized mAb against human VEGF, able to improve, in combination with carboplatin and paclitaxel, overall response and time to progression in patients with advanced or recurrent NSCLC, especially in nonsquamous cell histology [11]. The positive results of this phase II trial have encouraged the further development of this drug also in combination with other targeted agents, such as erlotinib. A phase I/II trial has been conducted in patient with nonsquamous advanced NSCLC, not previously treated with chemotherapy, by using the association of escalating doses of erlotinib and bevacizumab [12]. An overall response rate of 85%, including 20% of partial responses, has been reported, as well as an overall survival of 52% at one year and a progression free...
A promising agent is the orally available TKI ZD6474 kinase receptors and intracellular targets. Among them, selectively targeting one signalling protein, it has been proposed agent alone [13].

Along with the combination of EGFR inhibitors with agents selectively targeting one signalling protein, it has been proposed the use of drugs with multitargeting capability against several kinase receptors and intracellular targets. Among them, a promising agent is the orally available TKI ZD6474 (Zactima™). We have demonstrated that ZD6474 is a dual inhibitor of VEGFR-2 (KDR) and of EGFR and that, in cancer cells acquiring resistance to EGFR inhibitors and that use VEGF overexpression as escape pathway, ZD6474 can revert such resistance [14, 15]. ZD6474 has been evaluated in a phase II randomized placebo-controlled trial in combination with docetaxel in platinum refractory NSCLC, showing a manageable toxicity profile in combination with chemotherapy and an increase in progression free survival [16]. Recently, the results of a randomized, double-blind phase II trial of ZD6474 versus gefitinib in patient with chemorefractory recurrent NSCLC demonstrated a statistically significant advantage of ZD6474 over gefitinib in progression free survival (11.9 vs. 8.1 weeks) and in disease control (43 vs. 34 %) with comparable side effects between the two treatment [17]. Phase III studies in combination with chemotherapy are now ongoing to evaluate the efficacy of ZD6474 alone and in combination with chemotherapy.

Recent studies have shown a functional cross-talk between EGFR intracellular signaling and the COX-2 pathway [18], since EGFR activation induces COX-2 expression and prostaglandin E2 production in cancer cells [19]. Moreover, we have shown that COX-2 overexpression parallels VEGF increase in EGFR inhibitors resistant cells [15]. On this basis ZD6474 has also been assessed in association with cyclooxygenase-2 (COX-2) inhibitors in preclinical NSCLC models. The combination of ZD6474 and SC-236, a selective COX-2 inhibitor, is able to induce a prolonged growth inhibition of tumors in established lung adenocarcinoma A549 cancer xenografts compared to single agent therapy [20]. A clinical trial evaluating the combination of erlotinib and the COX-2 inhibitor celecoxib is ongoing in patients with advanced or recurrent NSCLC.

The possibility of using agents that can block several crucial pathways in human cancer cell lines is highly attractive, either with the combination of biological inhibitors directed against different specific targets, or with multitargeted drugs potentially offering the benefits of combined therapy within a single agent. However, it should be considered that combined effects observed with this approach make it difficult to establish the relative benefits of single-pathway targeting and could results in additive unexpected toxicity. The results of several clinical trials now ongoing will clarify some open issues regarding the combination of biological therapies in NSCLC.

references


