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Anti-Tumour Treatment

Targeted therapies for advanced non-small-cell lung cancer: Current status and future implications

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ABSTRACT

Lung cancer remains the leading cause of malignancy-related mortality worldwide, with over one million cases diagnosed yearly. Non-small-cell lung cancer (NSCLC) accounts for >80% of all lung cancers. Because lung cancer is typically diagnosed at an advanced stage, chemotherapy (CT) is the mainstay of management. Conventional treatment of NSCLC has apparently reached a plateau of effectiveness in improving survival of patients, and treatment outcomes must still be considered disappointing. Hence, considerable efforts have been made in order to identify novel targeted agents that interfere with other dysregulated pathways in advanced NSCLC patients. In order to further improve the results of targeted therapy, we should not forget that lung cancer is a heterogeneous disease with multiple mutations, and it is unlikely that any single signaling pathway drives the oncogenic behaviour of all tumours. The relative failure of some targeted therapies may be a result of multilevel cross-stimulation among the targets of the new biological agents along several pathways of signal transduction that lead to neoplastic events. Thus, blocking only one of these pathways allows others to act as salvage or escape mechanisms for cancer cells. We summarize the most promising research approaches to the treatment of NSCLC, with particular attention to drugs with multiple targets or combining targeted therapies.

Introduction

Non-small cell lung cancer (NSCLC) is a very lethal disease responsible for more than a million deaths worldwide each year.[1] Because it is typically diagnosed at an advanced stage, chemotherapy (CT) remains the cornerstone of treatment, with palliation and patientś quality of life as the primary end-points.

Although several advantages have been observed, palliative CT offers a median survival not exceeding 1 year and, to date, various combinations of cytotoxic drugs have not improved treatments results beyond what has been observed with platinum doublets.[2] In contrast, major progress in the understanding of cancer biology and the mechanism of oncogenesis has allowed the development of molecular targeted therapies that block dysregulated signaling pathways and the metabolic processes contributing to the acquisition of a cancer phenotype.[3,4] Better toxicity profile than conventional CT, target selectivity, availability for chronic treatment and, in some cases, oral administration have marked these targeted compounds as the most promising research drugs. Consequently, several targeted therapies have been introduced into clinical trials in NSCLC, both as single agents and combined with other conventional treatment modalities, such as CT or radiotherapy (RT).

Targeted inhibition of either the vascular endothelial growth factor receptor (VEGFR) or epidermal growth factor receptor (EGFR) signaling pathways has been clinically validated in advanced NSCLC, with a number of currently approved drugs (e.g., bevacizumab, erlotinib, cetuximab, gefitinib).[3–7] Furthermore, novel targeted therapies that interfere with other dysregulated key signaling pathways and molecules, such as insulin-like growth factor 1 receptor (IGF-1R), PI3K/AKT/mammalian target of rapamycin (mTOR), Ras/Raf/MAPK, MET kinase, proteasome, histone deacetylase (HDAC) or heat-shock proteins (Hsp) have been identified as potential targets.[8–11] Research efforts are currently focusing on tailoring such therapies according to predictive clinical characteristics and molecular biomarkers in attemps to individualize therapy.

Although these agents have had clinical success, dissapointing results have also been documented. It is now known that a matrix of interconnected and in some cases redundant signal transduction pathways is responsible for maintaining many solid tumors. Multilevel cross-stimulation exists among the targets of the new biological anticancer agents and molecular pathways involved in survival and replication of cancer cells are very complex. In fact, one of the main reasons for the relative failure of the first generation of clinical trials is that it is becoming increasingly evident that solid tumors have multiple salvage and resistance pathways that allow

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them to circunvent inhibition of a single signaling pathway. It is highly likely that lung cancer patients have several abnormalities and that agents with a single target will be insufficient for providing any meaningful therapeutic outcomes. Compared with inhibiting a single signaling pathway, inhibition of multiple signaling pathways may help maximize suppression of oncogenic processes involved in disease progression. Furthermore, it is important to introduce combination therapy early in the course of a disease to prevent the emergence of resistance. This become particularly true when those targeted pathways share common downstream effectors. Preclinical and clinical evidence of synergistic antitumor activity achievable by combining targeted agents that block multiple signaling pathways has recently been emerging.[12,13]

On the other hand, in addition to erlotinib and gefitinib, which specifically target the EGFR pathway, efforts to identify drugs that inhibit key pathways involved in the pathogenesis of NSCLC have led to the development of multi-targeted agents. Small-molecule tyrosine quinase inhibitors (TKIs) that inhibit receptors such as VEGFR-2, EGFR, platelet-derived growth factor receptor (PDGFR), Raf and KIT simultaneously may offer advantages over agents with single targets, and therefore a higher likelihood of single-agent activity.[14–16] In addition, because multi-targeted TKIs are often available orally, they may be more convenient for patients. However, a potential disadvantage is the possible toxicity of off-target kinase inhibition and the additional toxicity when the agents are combined with CT, which may be particularly relevant.

This review outlines the current state-of-the-art research for targeted therapy in NSCLC, performed using combinations of selective agents or agents that intrinsically block various targets.

Combined inhibition of VEGFR and EGFR signaling pathways

Rationale for dual inhibition of VEGFR and EGFR signaling in nsclc

Although several agents that individually target the EGFR or VEGFR pathways have been approved for use in advanced NSCLC, the activity of these agents as monotherapy is modest.[3–5,17] These finding suggest that the use of single-targeted therapies alone to inhibit either VEGF-dependent pathologic angiogenesis or EGFR-dependent tumor proliferation may be insufficient for optimal clinical effects.

Lung cancer is well established as a highly heterogeneous disease,[18] with multitude of cellular components and patterns of gene expression that affect prognosis and response to treatment.[19,20] This complicated nature makes it highly unlikely that the survival of the majority of tumors is dependent on a single mutation, signaling pathway or growth factor. Dual inhibition may be important for optimal suppression of solid tumor growth, because EGFR and VEGF share both parallel and reciprocal downstream signaling pathways, particularly with respect to angiogenesis.[21,22] For example, the activation of EGFR by epidermal growth factor (EGF), heregulin or transforming growth factor α (TGF-α) can upregulate the production of VEGF in human cancer cells, suggesting that the oncogenic properties of the EGFR-driven pathway may, at least in part, be mediated by the stimulation of tumor angiogenesis by upregulating angiogenic growth factors.[23–25] Conversely, some authors have provided evidence that EGFR blockade causes inhibition of the secretion of VEGF and other angiogenic growth factors, including basic fibroblast growth factor (bFGF), interleukin-8, and TGF-α.[23] Moreover, recent work have also demonstrated that inhibition of the downstream EGFR-mediated effector mTOR reduces VEGF expression and capillary tube formation by endothelial cells,[26] and that the K-ras downstream pathway may also play an important role in malignant transformation.[27] Thus, there is a rational to suggest that dual blockade of both EGFR and VEGFR pathways could provide an additive and even synergistic anticancer therapeutic strategy.

Additional support for the strategy of dual inhibition was demonstrated when it was found that combined inhibition of multiple targets has the potential to overcome resistance to monotherapies.[28] Although some patients initially respond to EGFR TKIs, nearly all eventually become refractory to treatment.[29] Several mechanisms may aid in the development of resistance, including second mutations leading to conformation changes in the TKI binding domain, ligand-independent activation or overactivity of downstream signaling pathways.[29–31] Alternatively, it has been proposed that an overactive VEGFR pathway independent of EGFR may play a role in resistance to EGFR-targeted therapies.[30] If this is the case, then dual inhibition of both pathways may act to prevent resistance through VEGFR. In addition, because evidence suggest that EGFR inhibitors may sensitize some tumor cells to conventional CT by blocking alternative escape routes, dual inhibition of EGFR and VEGFR signaling cascades may provide even greater chemosensitization.[30]

Clinical experience with combined inhibition of VEGFR and EGFR signaling pathways in the treatment of NSCLC is discussed below (Tables 1 and 2).

Bevacizumab and erlotinib

A number of preclinical and early clinical data provide a strong rationale for combined inhibition of both the VEGFR and EGFR pathways to achieve greater suppresion and possibly delay emergence of resistant tumors.[21,22,25,32] It had been proposed that a dual approach that targeted both the tumor (by inhibiting EGFR signaling) and the endothelial cells that would ultimately support growth of the tumor (by inhibiting VEGF) could be more effective.[33] Moreover, the lack of overlapping toxicities between inhibition of the VEGFR and the EGFR pathways suggests that simultaneous inhibition of both of them has the potential to be tolerated by lung cancer patients.[34,35]

Several clinical trials in NSCLC also support the idea of using multiple single-targeted agents to promote more beneficial antitumor effects. Because bevacizumab and erlotinib have demonstrated survival benefits in the first- and second/third-line setting, respectively,[4,5,17] there is interest in determining whether combining these drugs offers and additional benefit. A phase I/II study examined erlotinib and bevacizumab in patients with nonsquamous stage IIIB/IV NSCLC pretreated with one or more prior CT regimens.[36] In the phase I portion of the study, an erlotinib dose of 150 mg once daily orally plus a bevacizumab dose of 15 mg/kg iv every 21 days were established as the phase II dose, although no dose-limiting toxicities were observed. Phase II assessed the efficacy and tolerability of erlotinib and bevacizumab at this dose. Forty patients were treated (34 patients at phase II dose) and 22 had $\geqslant$2 prior regimens. The most common adverse events (AEs) were mild to moderate rash, diarrhea, and proteinuria. Eight patients (20%) had partial responses (PR) and 26 (65%) had stable disease (SD) as their best response. The median overall survival (OS) for the 34 patients treated at the phase II dose was 12.6 months, with progression-free survival (PFS) of 6.2 months. A second phase II study by the same authors evaluated the safety of combining bevacizumab with either CT (docetaxel or pemetrexed) or erlotinib and preliminary assessed these combinations versus CT alone, as measured by PFS.[37] One hundred and twenty patients with nonsquamous NSCLC that has progressed during or after one platinum-based regimen were randomly assigned and treated. No unexpected toxicities were observed. Fewer patients (13%) in the bevacizumab-erlotinib arm discontinued treatment as a result of AEs than in the CT alone (24%) or bevacizumab-CT arms (28%). Although not statistically significative, relative to CT alone, the risk