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Review

The role of new agents in the treatment of non-small cell lung cancer

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Abstract

Lung cancer is one of the most frequent causes of cancer deaths worldwide. Non-small cell lung cancer (NSCLC) accounts for approximately 80% of cases and no curative treatment is available for the advanced stages of disease (stages III and IV), which comprise the majority of cases. Current treatment regimens with standard chemotherapy offer only a limited survival benefit, and, therefore, the development of new therapeutic strategies is needed. Novel chemotherapeutic drugs such as the epothilones, MEN 10755 and S-1 are being studied in patients with advanced stages of disease. Furthermore, a large number of therapies targeted against critical biological abnormalities in NSCLC are being investigated in clinical trials. The latter approach includes inhibition of growth factors, interference with abnormal signal transduction, inhibition of angiogenesis and gene replacement therapy. Promising results have thus far been obtained with some of these therapies. This review describes the role of new therapeutic agents in the treatment of NSCLC.

Keywords: Lung cancer; New agents; Treatment; NSCLC

1. Introduction

Lung cancer is one of the most commonly occurring malignancies in the world and is the leading cause of cancer-related death in men. It is generally divided into small cell lung cancer (SCLC), which accounts for approximately 20% of all cases, and non-small cell lung cancer (NSCLC) that can be subdivided into squamous cell carcinoma, adenocarcinoma and large cell carcinoma and represents approximately 80% of all lung cancers [1].

Surgery remains the sole curative treatment modality for patients with NSCLC. However, less than one third of patients are candidates for surgical exploration and more than 50% of them will eventually relapse [2]. Chemotherapy is broadly used for advanced stages of NSCLC and usually consists of a platinum-containing compound (cisplatin or carboplatin) combined with gemcitabine, a taxane (paclitaxel or docetaxel) or vinorelbine [3]. A recent randomised study among 1207 patients showed that four platinum-based combination regimens were similarly effective with a response rate of 17–21% and a 1-year survival rate of 31–36% in previously untreated patients with stage IIIB or IV NSCLC [4]. When compared with best supportive care, chemotherapy offers only a limited survival benefit often at the cost of substantial toxicity [5,6].

Chemotherapy has not substantially altered the long-term outcome for most lung cancer patients in the past decade and it is likely that the results of chemotherapy have reached a plateau [7]. Therefore, novel treatment strategies are urgently needed in advanced NSCLC. New ways to improve the results of current treatment regimens appear to be the use of novel chemotherapeutic agents with more favourable toxicity and activity profiles and the use of biological agents that target for example abnormal signal transduction pathways, either alone or in combination with chemotherapy. This review describes the current status of novel biological and chemotherapeutic drugs for the treatment of NSCLC.

2. Novel chemotherapeutic agents in the treament of NSCLC

In general, there are not that many novel chemotherapeutic agents being developed. Most novel agents are in fact targeted to specific molecular alterations. However, here we will examine some of the more interesting

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agents with cytotoxicity as the major mechanism of action, which may have activity in NSCLC and be further developed for the treatment of this disease.

2.1. Epothilones

Taxanes are widely used in the treatment of NSCLC both as single agents (second-line) and in combination with other chemotherapeutic drugs such as cisplatin and carboplatin (first-line). However, a major drawback of this group of agents is the presence or the development of resistance. Drug resistance to taxanes is mostly due to upregulation of P-glycoprotein that can pump the drug out of the cell, or mutations in the cellular target, β-tubulin [8].

Epothilones are new compounds that are structurally unrelated to the taxanes, but have the same mechanism of action, and stabilise the microtubules more potently than paclitaxel [9]. Interestingly, the epothilones are not good substrates for P-glycoprotein and they are active in paclitaxel-resistant cell lines with certain β-tubulin mutations [9,10].

EPO906, an epothilone B analogue produced by Novartis Pharma AG, has been investigated in several phase I clinical trials, in which one objective response was observed in 31 patients with advanced solid tumours [11,12]. Another epothilone B-derivative, BMS-247550 produced by Bristol Myers Squibb, has also shown clinical activity in various phase I trials. Its side-effects consist of myelosuppression, neurotoxicity and gastrointestinal symptoms [13–15]. Preliminary results from a phase II trial with this agent when given as a single agent every three weeks in 22 advanced NSCLC patients who had failed first-line platinum-based chemotherapy, showed a response rate of 18% with stabilisation of disease in another 46% [16]. Furthermore, this agent proved to be effective in some taxane-refractory breast cancer patients [17]. These results indicate that the epothilones may provide a valuable contribution in the treatment of NSCLC.

2.2. Other new chemotherapeutic drugs

Glufosfamide is a new alkylating agent in which isophosphoramide mustard, the alkylating metabolite of ifosfamide, is linked to β-D-glucose [18,19], which leads to drug stabilisation and preferential uptake of the compound via the transmembrane transport system of glucose [20]. This targeting mechanism, together with the accelerated metabolic rate and increased glucose consumption of tumour cells, suggests potentially enhanced tumour selectivity for glufosfamide. Phase I trials in patients with advanced solid tumours demonstrated clinical activity with objective responses in several tumour types [21,22]. The dose-limiting toxicity of this agent consists of reversible renal tubular acidosis and other side-effects include neutropenia, nausea, vomiting and alopecia. In a phase II trial in 39 patients with advanced NSCLC, 3 partial responses among 31 assessable patients were observed after administration of this drug [23].

Anthracyclines have not been very active in NSCLC [24], but in recent years, novel anthracycline analogues have been developed, that have a broader activity and a more favourable toxicity spectrum [25]. Among these is MEN 10755, an anthracycline disaccharide, which is active in doxorubicin-resistant xenografts, including lung cancer models, and causes less cardiotoxicity than doxorubicin and epirubicin in preclinical studies [26–30]. Its side-effects consist of neutropenia and thrombocytopenia, and pharmacokinetic analysis revealed a shorter half time life and a much smaller volume of distribution than doxorubicin [31,32]. The clinical activity of MEN 10755 in NSCLC has been studied in phase II trials in patients with advanced stages of disease, but final results are not yet available.

S-1 is a novel oral fluoropyrimidine derivative consisting of tegafur (FT), a prodrug of 5-fluorouracil (5-FU), and two modulators, potassium oxanate and CDHP that inhibit the degradation of FT-derived 5-FU. In preclinical studies, this drug showed anti-tumour activity in a variety of tumours, including lung cancer models [33,34]. Side-effects of S-1 consist of gastrointestinal symptoms and myelosuppression in a few cases [35]. In a phase II study involving 59 NSCLC patients with advanced stages of disease, S-1 showed a response rate of 22% with a median response duration of 3.4 months, indicating that this drug may represent a valuable contribution to the treatment of NSCLC [36,37].

3. Biological drugs for NSCLC

3.1. Targeting erbB receptor pathways

Growth factor dependency drives cell proliferation and differentiation and it is now clear that tumour cells may overcome normal regulatory inhibition of proliferation by an enhanced or inappropriate activation of protein tyrosine kinases such as the erbB receptor family [38,39]. This family includes four distinct members: HER1 (Epidermal Growth Factor (EGF)-receptor or c-erbB1), HER2 (neu or c-erbB2), HER3 (c-erbB3) and HER4 (c-erbB4), which share an overall structure of two cysteine-rich regions in the extracellular domain and a cytoplasmic kinase pocket with a carboxy-terminal tail that is responsible for the diversified stimulation of downstream signal transduction pathways. However, HER3 lacks intrinsic kinase activity and no direct ligand has thus far been identified for HER2, which acts instead as a co-receptor [40–42]. Upon binding of the

ligand, the intracellular tyrosine kinase domain is activated, resulting in tyrosine autophosphorylation which ultimately triggers a cascade of diverse physiological responses involved in the mitogenic signal transduction of the cells [39,43,44].

It has been known for several years that the EGF-receptor (EGFR) is overexpressed in many lung tumours [39]. Squamous cell carcinomas overexpress EGFR most frequently (85%) and strongly, whereas adenocarcinomas and large cell carcinomas are positive in approximately 65% of cases (reviewed in [45]). Although some studies have showed that EGFR-expression may be correlated with a decreased survival [46–51], others have indicated that EFGR-expression is of no prognostic significance [52–58]. Her2/neu is overexpressed in approximately 25% of NSCLC (reviewed in [59]) and correlates with increased metastatic potential, drug resistance and poor prognosis [52,60–69]. Based on these molecular characteristics of NSCLC, several agents have been developed that target the erbB-receptor family [70]. A summary of studies in lung cancer with erbB-inhibitors is given in Table 1.

ZD1839 and OSI 774 are small molecules that target the HER1 receptor, and both have demonstrated single agent activity with objective responses in heavily pretreated NSCLC patients. They are well absorbed after oral administration and can be given chronically. Both drugs have similar side-effects that are usually mild to moderate and consist of dose-dependent acne-like skin rash and diarrhoea which represents the dose-limiting toxicity. Other adverse events include anorexia, nausea and a transient rise of the liver transaminases [71–76]. Recently, a large randomised phase II multicentre trial with two doses (250 and 500 mg/day) of ZD1839 has been reported in 210 stage III or IV NSCLC patients, who failed one or more prior treatment regimens. Side-effects were generally mild and consisted of skin rash, pruritus and diarrhoea, but were significantly more common and severe at the higher dose level. Remarkably, both dose levels were equally efficacious with response rates of 18.4 and 19%, respectively [77,78]. In another randomised phase II trial of 250 or 500 mg ZD 1839 in 216 patients with more extensive pre-treatment, response rates were 8.8–11.8% [79,80]. OSI 774 was investigated in a phase II trial in 56 patients with advanced NSCLC who failed prior platinum-based chemotherapy, and, unlike for the studies with ZD1839, were selected based on overexpression of EGFR ($\geqslant$10% positive cells). In this study, OSI 774 was given continuously at a fixed dose of 150 mg/day, which produced an acneiform rash in almost 80% of patients. The response rate was 11%, whereas 34% of patients had stable disease on this treatment [81].

In general, ZD1839 and OSI 774 do not induce myelosuppression, which makes them attracting for combination studies with chemotherapy. Moreover, *in vitro* and *in vivo* studies have shown that ZD1839 potentiates the effect of several chemotherapeutic agents [82,83]. Two large double-blind randomised studies with a combination of chemotherapy and ZD1839 have recently been completed, in which chemotherapy was added to 500 mg/day, 250 mg/day ZD1839 or to a placebo [84]. Both studies accrued over 1100 patients and investigated two different treatment regimens: carboplatin-paclitaxel, which is standard in North America and cisplatin-gemcitabine, which is more frequently employed in the rest of the world. Phase III trials of a similar design are currently underway using OSI 774 [84]. Final analysis of the ZD1839 studies is expected shortly and the results of these important trials will help

Table 1
Current trials with inhibitors of the erbB-receptor pathway in NSCLC

	Compound	Status	Trial design
Monoclonal antibodies			
HER1	C225	Phase II [96]	Carboplatin/paclitaxel plus C225, first-line in advanced NSCLC Gemcitabine/carboplatin plus C225, first-line in advanced NSCLC Docetaxel plus C225, second-line in advanced NSCLC
	ABX-EGF	Phase I	Dose-escalating study in patients with advanced solid tumours, including NSCLC [232]
	EMD72000	Phase I	Dose-escalating study in patients with advanced solid tumours, including NSCLC [233]
HER1–2	GW2016	Phase I	In progress [84]
HER2	Trastuzamab (Herceptin®)	Phase II	Chemotherapy +/−compound, first- and second-line in advanced NSCLC [100]
Small molecules			
HER1	ZD1839	Phase III, completed	Carboplatin/paclitaxel or gemcitabine/cisplatin +/−compound (two different doses), first-line in advanced NSCLC [84]
	OSI 774	Phase III	Carboplatin/paclitaxel or gemcitabine/cisplatin +/−compound, first-line in advanced NSCLC [84] Carboplatin/paclitaxel or gemcitabine/cisplatin +/−compound after 1–2 regimens in advanced NSCLC [84]
pan-erbB	CI-1033	Phase I-II	Dose-escalating studies in patients with advanced solid tumours, including NSCLC [234–238]

NSCLC, Non-small cell lung cancer. EGF, epidermal growth factor.

to define the role of these new agents in the management of NSCLC.

C225, a chimeric antibody that blocks the tyrosine kinase activity of the erbB1-receptor, has been most extensively studied in head and neck and colorectal cancers. In head and neck cancers C225 has demonstrated considerable activity when given in combination with cisplatin to patients that are refractory to this drug [85–88]. Similar results were obtained when C225 was given in combination with CPT-11 to colorectal patients who were progressive on CPT-11 [89–91]. C225 has a half-life of approximately 7 days and can be given weekly with a loading dose of 400 mg/m^2, followed by a maintenance dose of 250 mg/m^2. Side-effects include acne-like skin rash, asthenia, and allergic reactions which occur in up to 4% of cases [92]. In preclinical NSCLC models, C225 was shown to potentiate the effect of chemotherapy and radiotherapy [93–95]. Phase II clinical trials in advanced NSCLC are ongoing to evaluate the efficacy and tolerability of combinations with chemotherapeutics [96]. Preliminary results from a combination study with docetaxel show clinical activity with objective responses in 4 out of 20 patients with mild to moderate side-effects [97].

Trastuzamab (Herceptin®), a humanised monoclonal antibody that binds to HER2, is registered for the treatment of breast cancer, in which it reached a response rate of 15% as single agent therapy in HER2-overexpressing tumours, which comprise 25–30% of breast cancers [98,99]. Side-effects consist of cardiac dysfunction in a few cases, which is worrying when trastuzamab is given in combination with anthracyclines [99]. Since HER2 is expressed in 20–66% of NSCLC, several trials have now been conducted to evaluate its effect in this tumour type [100]. However, the level of expression of HER2 is lower in NSCLC than in breast cancer, which makes the selection of patients rather cumbersome. In an Eastern Cooperative Oncology Group (ECOG) study in 139 patients with NSCLC, 50 patients were found to be HER2-negative, whereas only 9% of patients were strongly positive [101]. Krug and colleagues found even fewer patients showing overexpression of HER2: among 84 patients screened, HER2 was 3+ in only 6 patients and a total of 19% were 2 or 3+ [102]. In this phase II trial, previously untreated patients received trastuzamab with either docetaxel or paclitaxel. The overall response rate was 26% and did not differ significantly according to the HER2 status (overexpression 20 vs. 28% in others). To evaluate the effect of trastuzamab more closely, a randomised trial was conducted, using either trastuzamab plus gemcitabine and cisplatin, or gemcitabine and cisplatin alone [103]. Among 103 patients, the overall response rates in the control and trastuzamab arms were 41.2 and 36%, respectively, indicating that trastuzamab was not likely to add any benefit to the standard therapy. However, only very few patients with strongly HER2-positive disease were included in this trial. This problem makes the investigation of the potential effect of trastuzamab in NSCLC particularly difficult, since this drug does not seem to be effective in patients that do not have a high expression of HER2 [104]. Activity may be limited to cases that are strongly HER2 (3+) and/or fluorescent *in situ* hybridisation (FISH) positive.

3.2. Farnesyltransferase inhibitors

Post-translational modifications of proteins by the addition of a farnesyl group is critical for the function of a number of proteins involved in signal transduction. The best-studied proteins in this respect are probably the Ras proteins that play pivotal roles in the control of normal and transformed growth [105,106]. In approximately 25–30% of all adenocarcinomas, mutations are present in *Ras* genes leading to the production of mutated proteins that remain in a locked, active state thereby relaying uncontrolled proliferative signals [107,108]. Essential for Ras-activity is the transfer of farnesyl isoprenoid to the cytoplasmic Ras c-terminus, a process catalysed by an enzyme called farnesyltransferase. This understanding has led to the development of farnesyltransferase inhibitors (FTIs) that block the growth stimulating and regulatory effects of Ras. Additionally, FTIs affect many other proteins, such as Rho, Rheb and CENP-E and F, that need to be farnesylated for their growth regulatory function [109].

The FTIs can be divided into three groups: farnesyl diphosphate (FDP) analogues, which compete with FDP, the substrate for farnesyltransferase; CAAX-mimetics that target the CAAX-portion of the Ras-protein, and agents which combine features of both. Drugs that are in current clinical investigation, BMS 214662, SCH 66336, R115777 and L778,123, all belong to the second class [110]. Side-effects of these agents include gastrointestinal toxicity, fatigue and, less frequently, myelosuppression. Biological studies have shown decreased farnesyltransferase activity in normal tissues and tumour cells after intravenous (i.v.) administration [111–117]. In a phase I setting, three partial responses in solid tumours were seen after treatment with SCH 66336, and one patient with NSCLC responded to this agent [111,118]. Although R115777 has demonstrated clinical activity in acute myeloid leukaemia (AML) and glioma patients, no responses were observed in a phase II trial in 44 patients with NSCLC [119–121]. Similarly, L778–123 was not effective in 23 patients with this tumour type [113]. Combination studies of FTIs with chemotherapeutic drugs are underway in NSCLC. A large phase III trial is about to start with carboplatin/paclitaxel plus SCH 66336 versus placebo in untreated NSCLC patients.

3.3. Inhibition of angiogenesis

Growth of new blood vessels is required for solid tumours to expand beyond a volume of 1–2 mm^3 [122]. This process of angiogenesis is regulated by a balance between pro- and anti-angiogenic factors: vascular endothelial growth factor (VEGF), basic and acidic fibroblast growth factor (bFGF and aFGF), platelet-derived endothelial growth factor (PD-ECGF) and others stimulate neovascularisation [123], whereas angiostatin [124], endostatin [125] and thrombostatin [126,127] are important inhibitors of this process. Increased tumour angiogenesis, identified by increased microvessel density and VEGF and PD-ECGF-expression, is associated with a worse clinical outcome in many solid malignancies, including NSCLC [128–136].

The fundamental goal of anti-angiogenic therapy is to induce a 'dormancy state' of primary tumours and their (micro) metastasis by returning foci of proliferating microvessels to their normal resting state and preventing their re-growth [137]. Clinical responses induced by anti-angiogenic agents may therefore primarily be expected from their combination with chemotherapy [138]. Inhibition of angiogenesis is actively under study in NSCLC (Table 2). Rhumab-VEGF (bevacizumab), a recombinant humanised antibody against VEGF, has been administered in human studies as a single agent and in combination with chemotherapy. Side-effects associated with the VEGF-antibody were generally mild and consisted of headache, asthenia, low-grade fever, arthralgia, nausea, vomiting and skin rash [139,140]. In a randomised phase II trial in 99 chemotherapy-naïve patients with advanced NSCLC, the effect of two different doses of anti-VEGF (7.5 mg/kg and 15.0 mg/kg) plus carboplatin/paclitaxel was compared with carboplatin/paclitaxel alone [141]. Patients treated at the higher dose of Rhumab-VEGF experienced a higher response rate than the patients treated at the lower dose or with chemotherapy alone (34.3 versus 21.9 and 25%, respectively). Additionally, time to progression was longer in this group (207 versus 124 and 181 days, respectively). However, six episodes of life-threatening haemoptysis were observed, four of which were fatal. Furthermore, several episodes of non-life-threatening epistaxis were seen in patients receiving Rhumab-VEGF (31 and 44% in the high and low dose arms, respectively). Remarkably, pulmonary haemorrhage was most common in patients with squamous cell histology and central, cavitated tumours, whereas it was relatively mild in two patients with non-squamous cell carcinoma [142]. A subset analysis of 78 patients with non-squamous cell carcinoma showed very promising results with median survival times of 77 versus 61 and 53 weeks in patients treated with high dose Rhumab-VEGF versus low dose Rhumab-VEGF and chemotherapy alone, respectively [143]. Based upon these results, ECOG initiated a phase III study of chemotherapy plus high dose anti-VEGF (15 mg/kg) versus chemotherapy alone in advanced non-squamous cell NSCLC [144].

Another anti-angiogenic drug that has been actively investigated is SU5416, a synthetic antagonist of the VEGF-receptor type 2, Flk-1/KDR. This agent specifically inhibits the phosphorylation of Flk-1 that occurs in response to binding of its ligand VEGF, thereby inhibiting *in vitro* proliferation of endothelial cells and growth of *in vivo* models, including lung tumours [145–147]. Side-effects of this agent consist of nausea, projectile vomiting, headache, phlebitis and allergic reactions, possibly due to the vehicle cremophor® [148–150]. Responses after administration as a single agent were seen in squamous cell carcinoma of the head and neck and in AML [151,152]. In a feasibility study, two dose levels of SU5416, 85 and 145 mg/m^2, given in combination with full doses of gemcitabine and cisplatin were investigated [153]. Besides the expected side-effects of chemotherapy and SU5416, a worrying increase of thromboembolic events was observed. In a total of 19 patients with advanced solid tumours, 9 thromboembolic events were recorded in 8 patients. The explanation of these effects remains unclear, but may involve disturbances in the coagulation cascade and interaction

Table 2
Clinical studies with anti-angiogenesis agents in NSCLC

Drug	Mechanism	Status	Trial design
Rhumab-VEGF	VEGF-antagonist	Phase III	Carboplatin/Paclitaxel +/−Rhumab-VEGF in advanced non-squamous carcinoma [144]
Thalidomide	TNFα-antagonist	Phase III	Carboplatin/Paclitaxel followed by radiotherapy +/−thalidomide in stage III NSCLC [144]
SU5416	Inhibitor of Flk-1 receptor signalling	Phase I, closed	Studies closed because of unfavourable toxicity and activity profile
Squalamine	Inhibits sodium-hydrogen pump (isoform NH3)	Phase II	Carboplatin/paclitaxel plus squalamine in advanced NSCLC [239]
TNP-470	Fumagillin analogue, broad anti-angiogenic activity	Phase I	Three arm study: TNP-470 continuous infusion in advanced NSCLC +/−Carboplatin/Paclitaxel and +/−bolus TNP-470 [240]

VEGF, vascular endothelial growth factor. TNFα, tumour necrosis factor α.

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