Sorafenib in Non-Small Cell Lung Cancer—Results of Clinical Trials

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Abstract

Non-small lung cancer (NSCLC) patients with metastatic disease have a poor prognosis and platinum-based chemotherapy is the only treatment option in the majority of these patients. There is a great need for new targeted therapies in this complex and heterogeneous disease. Sorafenib is a multi-target tyrosine kinase inhibitor (TKI), which inhibits proteins involved in proliferation and angiogenesis and could be an attractive agent for patients with NSCLC. Sorafenib is studied in first- and second-line treatment as mono and combination therapy. In phase III trials, sorafenib failed to show improvement in survival as first-line treatment in addition to chemotherapy and as monotherapy in third or fourth line. Even detrimental effects were observed in patients with squamous histology. Still, a subgroup of patients derive long-term benefit from treatment with sorafenib. To identify these patients, biomarker studies have been conducted, but no predictive biomarker has yet been found. Combination therapy of sorafenib with other targeted agents is currently being studied.

Development of targeted treatment strategies is a matter of the utmost importance to improve clinical outcome measures in cancer. In non-small cell lung cancer (NSCLC), subgroups have been identified that respond well to treatment with tyrosine kinase inhibitors (TKIs) (e.g. erlotinib for epidermal growth factor receptor [EGFR]-mutated patients and crizotinib for patients with an EML4-ALK translocation).[1,2] Although platinum-based chemotherapy remains the first and only choice of treatment for the majority of NSCLC patients. Sorafenib, an oral multi-target TKI, has antiproliferative properties as well as antiangiogenesis properties. Therefore, sorafenib is a possible attractive agent for the treatment of cancer. Sorafenib has been developed as a target of Raf protein, but also inhibits several other receptor tyrosine kinases and proteins. Most importantly, sorafenib inhibits vascular endothelial growth factor receptors 1, 2 and 3 (VEGFRs 1,2,3), platelet-derived growth factor receptor-beta (PDGFR ß), RET, Flt3, and c-KIT. In phase II studies sorafenib monotherapy was found active in several types of cancer, including malignant lymphoma, melanoma, renal cell cancer (RCC), and hepatocellular cancer (HCC).[3–6] In randomized phase III trials, sorafenib showed improved outcome in HCC and RCC compared with placebo and in these cancers sorafenib is approved as second-line treatment. In other types of cancer, no clinical application has been found yet. In this article, an overview will be given on the place of sorafenib treatment in NSCLC and its future perspectives.

Sorafenib in Unselected NSCLC (see *Table 1*)
Sorafenib Monotherapy
Sorafenib as monotherapy has been studied in first- and second-line treatment. Phase II studies in second-line treatment demonstrate activity in patients with advanced NSCLC. In a multicenter phase II study, 52 advanced pretreated NSCLC patients received sorafenib monotherapy.[7] The primary endpoint was to measure response rate (RR). No partial responses (PRs) were observed, but 59% of the patients had stable disease (SD). Median progression-free survival (PFS) was 2.7 months and median overall survival (OS) was 6.7 months. In a discontinuation phase II study, previously treated NSCLC patients who had SD after 8 weeks of treatment with sorafenib were randomized to further treatment with sorafenib or placebo.[8] The primary endpoint was disease control rate (DCR) 2 months after randomization. Before randomization, 299 patients received sorafenib for 8 weeks—patients who responded continued sorafenib; patients that progressed went off study. In total, 81 patients with SD were randomized to receive sorafenib or placebo. The 2-month DCR after randomization was 54% and 23% for patients receiving sorafenib and placebo, respectively (p=0.005). The PFS was 3.3 months for patients receiving sorafenib versus 2.0 months in the placebo group (hazard ratio [HR] = 0.51, 95% confidence interval [CI] 0.30, 0.87; p=0.014). Although a trend in improvement in OS was observed (13.7 months versus 9.0 months, respectively) (HR=0.67, 95% CI 0.40–1.11; p=0.117) this was not significant, but this study was not powered to detect a survival difference. As sorafenib was found to have some efficacy in these two studies the compound was further investigated in a phase III trial. The MISSION trial, a phase III study in advanced non-squamous NSCLC patients, randomized 703 patients to receive sorafenib monotherapy or placebo as a third- or fourth-line therapy.[9] Primary endpoint was OS. The overall response rate (ORR) (p<0.0001) and DCR (p<0.0001) was significantly better in patients who received sorafenib compared with

Table 1: Sorafenib in Non-Small Cell Lung Cancer

Trials	Phase	N	Primary Endpoint	Treatment	ORR	DCR	Median PFS* HR	Median OS* HR	Comments
Monotherapy									
First line									
Dy et al.[10]	II	25	ORR	Sorafenib	12%	26%	2.8	8.8	Study failed to meet its primary endpoint
Second line									
Blumenschein et al.[7]	II	52	ORR	Sorafenib	0%	59%	2.7	6.7	
Wakelee et al.[8]	II	81	DCR	Sorafenib versus placebo		54%	3.3	13.7	
Combination therapy									
First line									
ESCAPE et al.[12]	III	926	OS	CP and sorafenib versus CP alone	27.4% versus 24.0%; p=0.10	50% versus 56%	4.6 versus 5.4 HR=0.99 (NS)	10.7 versus 10.6 HR 1.16 (NS)	Trial failed to meet its primary endpoint
NexUS et al.[13]	III	772	OS	Cis/gem and sorafenib versus cis/gem alone	28% versus 26%; p=0.27	62% versus 63%; p=0.39	6.0 versus 5.5 HR=0.83; p=0.008	12.4 versus 12.5 HR=0.98; p=0.401	Trial failed to meet its primary endpoint
Lind et al.[16]	II	50	DCR	Sorafenib and erlotinib	24%	74%	5.0	10.9	
Gridelli et al.[18]	II	60	1-year survival rate	Sorafenib and erlotinib versus erlotinib and gemcitabine	10.3% versus 6.5%	44.8% versus 42.0%	12.7 versus 8.1 weeks	12.6 versus 6.6	
Second line or more									
Spigel et al.[17]	II	168	ORR and PFS	Sorafenib and erlotinib vs placebo and erlotinib	8% vs 11%; p=0.56	54% versus 38%	3.38 versus 1.94 HR= 0.86; p=0.196	7.62 versus 7.23 HR=0.89; p=0.290	Combination of sorafenib and erlotinib showed PFS benefit in EGFR wt patients
MISSION et al.[9]	III	703	OS	Sorafenib versus placebo	p<0.0001	p<0.0001	2.8 versus 1.4 HR=0.60; p<0.0001	8.2 versus 8.3 HR=0.99; p=0.47	Not yet published

*Progression-free and overall survival (PFS/OS) in months. CP = carboplatin/paclitaxel; cis/gem = cisplatin/gemcitabine; DCR = disease control rate; EGFR = epidermal growth factor receptor; HR = hazard ratio; NS = not significant; ORR = overall response rate; OS = overall survival; wt = wild type.

patients who were treated with placebo. Median PFS in the sorafenib arm was 2.8 months versus 1.4 months in the placebo arm (HR=0.60 95% CI 0.51–0.72; p<0.0001). However, sorafenib showed no increase in OS compared with placebo (8.2 versus 8.3 months, respectively; HR=0.99 95% CI 0.84–1.17; p=0.47). Although this was a placebo-controlled study in the third and fourth line of treatment, some of the patients received post-study treatment. This might have negative impacted on the OS data. A phase II study of sorafenib as first-line treatment in advanced NSCLC was preliminary closed.[10] It failed to meet prespecified criteria in at least two responses in the first 20 patients after 8 weeks of treatment. Nevertheless, sorafenib had shown some activity with a RR of 12% in the 25 participating patients. In conclusion, sorafenib monotherapy failed to demonstrate benefit in unselected NSCLC patients, both in the first-line setting as well as in pretreated patients; however, in these trials some achieved long-term disease control, and, equally importantly, it was shown that long-term treatment with sorafenib was tolerable and no safety problems were encountered.[11]

Sorafenib and Chemotherapy Combinations

Sorafenib was also studied in combination with several cytotoxic agents. In two phase III trials conducted in patients with NSCLC, the addition of sorafenib to carboplatin and paclitaxel (Evaluation of Sorafenib,

Table 2: Sorafenib in KRAS-mutated Patients

Trials	Phase	N	Primary Endpoint	KRAS Mutation (%)	Response Compared with KRAS wt?	Survival Benefit?	Comments
Kim et al.[20]	II	341	DCR	20%	Higher	NR	105 patients received sorafenib
Kelly et al.[21]	II	37	ORR	32%	Equal	No	
MISSION trial[9]	III	703	OS	28%	Equal	No	KRAS mutation analysis was performed in 71 tumor samples
Dingemans et al.[22]	II	57	DCR	100%	NA	NA	Sorafenib was found active, further study in this selected group is warranted

DCR = disease control rate; NA = not applicable; NR = not registered; ORR = overall response rate; OS = overall survival; wt = wild type.

Carboplatin, and Paclitaxel Efficacy [ESCAPE] trial)[12] or to cisplatin and gemcitabine (NSCLC Research Experience Utilizing Sorafenib [NexUS] trial)[13] as front-line chemotherapy did not show an improvement in OS. In the ESCAPE trial, 926 NSCLC patients were randomized between placebo and sorafenib in addition to carboplatin and paclitaxel. The study was preliminary terminated after a prespecified interim analysis that showed a median OS of 10.7 months in the sorafenib arm versus 10.6 months in the placebo arm. Patients with squamous cell carcinoma (n=223) in the sorafenib arm had a shorter median OS than patients in the placebo arm (8.9 months versus 13.6 months, respectively; HR=1.85 95% CI 1.22–2.81). The OS and PFS in patients with nonsquamous histologies were similar in both arms. The RR was also similar in both arms. The ORR was 27.4% in the sorafenib arm and 24.0% in the placebo arm (p=0.1015).[17] In the NexUS trial, 772 nonsquamous NSCLC patients were randomized to receive sorafenib or placebo in addition to cisplatin and paclitaxel. Again, this study failed to show survival benefit in patients treated in the sorafenib arm compared with patients in the placebo arm (median OS 12.4 versus 12.5 months, respectively; HR=0.98 95% CI 0.83–1.16; p=0.401). The median PFS in the sorafenib and placebo groups was 6.0 months (95% CI 5.5–6.8 months) and 5.5 months (95% CI 5.1–5.7 months), respectively (HR 0.83; 95% CI 0.71 to 0.97; p=0.008). The ORR was 23% in the sorafenib arm and 28% in the placebo arm (p=0.11).

Sorafenib Combined with Other Small Molecules

Preclinical studies and phase I studies revealed synergism by inhibition of both VEGFR and EGFR.[14,15] Dual inhibition in theory has the potential to overcome resistance to EGFR TKI monotherapy. The combination of sorafenib and erlotinib, a EGFR TKI, showed activity in phase II studies. In a single-arm phase II study, 50 chemonaïve NSCLC patients were treated with erlotinib and sorafenib.[16] This combination was found active with a DCR at 6 weeks of 74%: 12 (24%) PRs and 25 (50%) patients had SD as their best response. Median PFS was 5.0 months, median OS was 10.9 months. The toxicity level was acceptable. In a second phase II study of sorafenib and erlotinib, 168 pretreated advanced NSCLC patients were randomized to sorafenib and erlotinib or erlotinib and placebo.[17] ORRs for sorafenib/erlotinib and placebo/erlotinib were 8% and 11%, respectively (p= 0.56), the PFS and OS were equally similar. In 72 patients EGFR mutational analysis was performed. In the 67 patients with EGFR wild type (wt), the median PFS was significantly better in the group treated with sorafenib and erlotinib (3.4 months for sorafenib/erlotinib versus 1.8 months for placebo/erlotinib (HR=0.56 95% CI 0.32–0.97; p= 0.018).

Median OS was 8.1 months for sorafenib/erlotinib versus 4.6 months for placebo/erlotinib (HR=0.53 95% CI 0.29–0.98; p=0.019). A slight increase in toxicities in sorafenib-treated patients was observed. Both studies encourage further evaluation of the combination of sorafenib and erlotinib in EGFR wt patients.

In elderly patients with advanced NSCLC the combination of sorafenib and erlotinib was found to be more feasible as first-line treatment than sorafenib and gemcitabine. Sixty patients were included in this phase II study. The primary objective was 1-year survival rate. The ORR was 6.5% for the combination of gemcitabine plus sorafenib and 10.3% for the combination of erlotinib plus sorafenib. The combination of sorafenib and erlotinib had a numerically higher 1-year survival rate than patients receiving sorafenib and gemcitabine. (45% versus 32%, respectively).[18] The synergistic effect of sorafenib and erlotinib has also been described in a preclinical study and gives rationale for future studies.[19]

Sorafenib in Selected Patients (see *Table 2*)

Sorafenib was suggested to have increased activity in NSCLC with a KRAS mutation. The BATTLE study is a biomarker-based adaptively randomized study that treated 158 pretreated NSCLC with erlotinib, vandetanib, erlotinib+bexarotene, or sorafenib according to predefined biomarkers—among others—EGFR and KRAS mutational status.[20] Patients with a KRAS mutation receiving sorafenib had the highest DCR of 79% (11/14 patients) compared with a DCR of 39% (nine of 23 patients) in patients with an EGFR mutation. This study suggests that patients with a KRAS mutation may benefit from treatment with sorafenib, although the trial result was not significant. However, a small single-centre study aimed at biomarkers that could predict response to sorafenib did not find benefit in patients with either a KRAS or EGFR mutation compared with patients without these mutations.[21] In line with this result, a subset analysis of the MISSION trial in KRAS-mutated patients did not show benefit for treatment with sorafenib.[11] The RAS/RAF pathway is overactive in KRAS-mutated NSCLC and could therefore be more sensitive to sorafenib, because of its ability to inhibit RAF. This hypothesis provided the rationale for a single-arm phase II study of sorafenib in NSCLC patients with a KRAS mutation performed by our group.[22] In total, 57 patients were treated with single-agent sorafenib. Primary endpoint was DCR at 6 weeks of treatment. After 6 weeks, five patients had a partial reponse (PR) (8.8%), 25 patients SD (43.8%), and 27 patients PD (47.4%), according to Response Evaluation Criteria In Solid Tumors (RECIST). We concluded that sorafenib was active

in this selected group of patients, with a DCR of 53%. However, survival was unsatisfactory, with a PFS of 2.3 months (95% CI 1.6–3.0 months) and an OS of 5.3 months (95% CI 3.6–7.0 months). Garassino et al.[23] demonstrated in vitro sensitivity of KRAS G12D mutation to sorafenib in NSCLC. G12C and G12V mutations were associated with resistance suggesting that types of KRAS mutations react differently to treatment. This finding is supported by a study of Ihle et al.[24] that demonstrate differences in downstream pathways KRAS subtypes. Whether there is a clinical relevant difference between types of KRAS mutation is should be further studied.

Biomarkers and Sorafenib Outcome

In unselected patients with NSCLC no benefit was observed during treatment with sorafenib, either as a single agent or in combination with cytotoxic chemotherapy. As sorafenib is a multi-targeted TKI also targeting angiogenesis, plasma angiogenic biomarkers may predict which patients will respond to sorafenib. An exploratory study was performed in 37 patients enrolled in a single-arm sorafenib monotherapy study.[21] Eleven of 34 patients with available tissue had a KRAS mutation and five of 34 had an EGFR mutation—no relation was observed with response to sorafenib. In addition, blood biomarkers were assessed. Low baseline basic fibroblast growth factor (bFGF) plasma levels were related to longer PFS and OS. In another study of 52 patients treated with sorafenib monotherapy, plasma levels of several angiogenic factors were studied at baseline, day 15 and day 1 of cycle 3.[7,25] Elevated baseline levels of VEGF, VEGF-165, Platelet-derived growth factor subunit B (PDGF-B), Ras p21, and tissue inhibitor of metalloproteinases 1 (TIMP-1) were related with shorter OS and PFS. Changes in these levels during treatment (especially increase in VEGF, VEGF-165, PDGF-BB, and TIMP-1) were related to better outcomes. The VeriStrat serum proteomics assay predicted improvement of PFS in the phase II study of sorafenib monotherapy in KRAS-mutated NSCLC patients.[22] In this assay, patients were assigned to two groups ('good' or 'poor') based on serum proteomics. Patients with a good prediction had a significantly superior median PFS than patients with poor prediction (2.6 versus 1.5 months, respectively; HR=1.4 95% CI 1.0–1.9; p=0.029). No prognostic value of VeriStrat was found (6.0 versus 2.5 months, respectively; HR=1.3 95% CI 0.9-1.7; p=0.166). The VeriStrat assay was also identified as prognostic and predictive biomarker for treatment with an EGFR TKI.[26-28]

Sorafenib and Imaging

It is known that predicting response by RECIST might underestimate response to drugs targeting angiogenesis as frequently tumor cavitation is observed instead of tumor shrinkage.[29] Dynamic contrast enhanced MRI (DCE-MRI) arguably provides more information on change in tumor vascularity during treatment with anti-angiogenic agents. In a single arm study with sorafenib monotherapy 26 of 37 patients underwent a DCE-MRI at baseline and at day 14.[21] Several DCE-MRI-derived parameters were assessed: Kep, the reverse contrast transfer rate; Ktrans, the forward contrast transfer rate; and Ve, the extravascular fraction. Patients with a small difference of Kep between baseline and day 14 had a longer OS and PFS compared with patients with a large difference. The other markers investigated were not associated with outcome. Given the small sample size, these outcomes should be regarded as exploratory. In our own phase II study of sorafenib and erlotinib we investigated the role of contrast-enhanced chemotherapy (CE-CT) in 23 patients.[30] We demonstrated that tumor blood flow as assessed by CE-CT decreased between baseline and weeks 3 and 6. In patients who responded according to both RECIST and Crabb[31] criteria, lower tumor blood flow was observed at week 3 and 6 than in the nonresponders; furthermore, patients with a tumor blood flow lower than the median tended to a longer PFS.

Discussion

Sorafenib, a multi-target TKI, is an attractive agent in a complex disease such as NSCLC. Looking at the targets of sorafenib there is a good rationale for clinical studies. Targeting VEGFR has proved to be effective when bevacizumab (an anti-VEFR monoclonal antibody) is added to conventional chemotherapy.[32,33] However, the use of sorafenib in combination with standard chemotherapy in NSCLC was not found to be more efficacious. Furthermore, treatment of sorafenib through inhibition of Raf protein has potential. As discussed previously, Raf protein has an important role in growth signalling. However, in NSCLC patients with a KRAS mutation, who have a hyperactivation of the Ras /Raf axis, treatment with sorafenib did not produce convincing results. Combination therapy of sorafenib with other agents has perspectives. Treatment with sorafenib and erlotinib in first or second line has rational to be studied further in EGFR wt patients. Also, preclinical studies report synergism in dual inhibition of the Ras/Raf pathway and PI3K/mTOR pathway. Clinical trials are ongoing with inhibitors of both pathways. No definitive biomarker predicting response to sorafenib has been found until now, although exploratory studies showed some markers of interest. Furthermore early response assessment by newer imaging techniques might select patients who benefit from sorafenib. For future studies it seems important to initiate clinical trials in selected patients instead of testing targeted treatment in all-comers. Sorafenib as monotherapy has modest activity in patients with NSCLC. Its application in combination with other agents is currently under investigation. Until now, sorafenib is not approved for treatment of NSCLC. ■

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