The Current Status and Evolving Role of Sunitinib in Non-small Cell Lung Cancer

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Abstract: Sunitinib, a small molecule, is a multitargeted receptor kinase inhibitor which targets the vascular endothelial growth factor receptor and platelet-derived growth factor receptor as well as several others. Initially approved for the treatment of renal cell carcinoma as well as imatinib-resistant gastrointestinal stromal tumors, the activity of sunitinib has been explored in several other solid tumors including non-small cell lung cancer (NSCLC). An initial phase II trial in 63 previously treated NSCLC patients using a dose of 50 mg daily 4 of 6 weeks showed a response rate of 11.1% and a stable disease rate of 26.8%. The median time to disease progression and overall survival was 12.0 and 23.4 weeks, respectively. The principal toxicities included fatigue, pain, myalgias, nausea/vomiting, and hypertension. Three hemorrhagic deaths were reported (two pulmonary and one central nervous system). After this trial was completed, a subsequent sequential cohort of 47 previously treated NSCLC patients were treated on a continuous dosing schedule of sunitinib at 37.5 mg daily. A response rate of 2.1% was reported with a stable disease rate of 19.X%. The median time to progression was 12.3 weeks with a median survival time of 38.1 week. Toxicities were, in general, less frequent and similar to those noted in the initial trial. Sunitinib is currently being evaluated in combination with a number of standard regimens commonly used in NSCLC as well as a maintenance drug after first-line platinum-based treatment of advanced NSCLC. Results of these trials are eagerly awaited and will help define the role of sunitinib in the therapeutic approach to NSCLC.

Key Words: VEGFR, PDGF, Receptor tyrosine kinase inhibitor.

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Sunitinib is a small molecule (Figure 1) that inhibits several members of the receptor tyrosine kinase (RTK) family, including vascular endothelial cell growth factor (VEGF) receptors types 1 and 2, platelet-derived growth factor (PDGF) receptors α and β, CSF-1R, c-KIT, FLT3, and RET.[1] RTKs are transmembrane proteins that transduce extracellular signals to the cytoplasm. Stimulation of these receptors results in cell proliferation and angiogenesis and enhances the metastatic potential of the malignant cell.[2,3] Successful inhibition of these RTKs has the potential to significantly alter the course of any hematologic or solid tumor malignancy where cell proliferation, angiogenesis, and metastasis are mediated by these RTKs.[4]

VEGF is one of the principal proangiogenic factor used by solid tumors to promote angiogenesis.[3,4] PDGF is upregulated during tumor progression, thereby stimulating the proliferation of pericytes and fibroblast needed to support the growing neovasculature.[4] PDGF has 2 receptors, α and β, which are frequently overexpressed in many solid tumors and their surrounding stoma,[2,5] Basic fibroblast growth factor and its receptor are expressed in many solid tumors and appear to be involved in promoting their growth.[6] Recent studies have suggested that both VEGF and PDGF play an important role in non-small cell lung cancer (NSCLC).[6–8] Elevated expression of VEGF is a strong prognostic indicator in NSCLC and is associated with early relapse and decreased survival in early-stage NSCLC.[6] Increased expression of PDGF has also been shown to be associated with a poor prognosis in NSCLC.[7] In addition, these pathways may cooperate in neoangiogenesis as was suggested by Shikada et al.[8] Given these data, the VEGF and PDGF pathways may be key targets in NSCLC, making therapies directed at these pathways a rational approach in this disease.[1]

Sunitinib is currently approved in the United States for the treatment of advanced renal cell carcinoma and imatinib-refractory gastrointestinal stromal tumors. As noted above, sunitinib is an inhibitor of both the VEGF and PDGF pathways and has shown clinical activity in renal cell carcinoma, gastrointestinal stromal tumors, breast cancer, and other solid tumors. In phase 1 trials, the initial dosage identified for use in most phase 2 trials was 50 mg/d orally for either 2 or 4 weeks followed by a 2-week rest period (2/2 and 4/2 schedule, respectively).[9] Sunitinib is metabolized by the CYP3A4 pathway to the active metabolite, SU012662.[9,10] Clearance is predominantly via the hepatic/biliary elimination.[9,10] The half-life of sunitinib is approximately 40 hours, whereas that of SU012662 is approximately 80 hours.[11] Because of these long half-lives, rest periods were incorporated in the original schedules, allowing recovery from the common toxic effects of sunitinib, which included fatigue, diarrhea, nausea, mucositis, hypertension, myelosuppression, and skin abnormalities.[9–11] The observation in preclinical models that tumor

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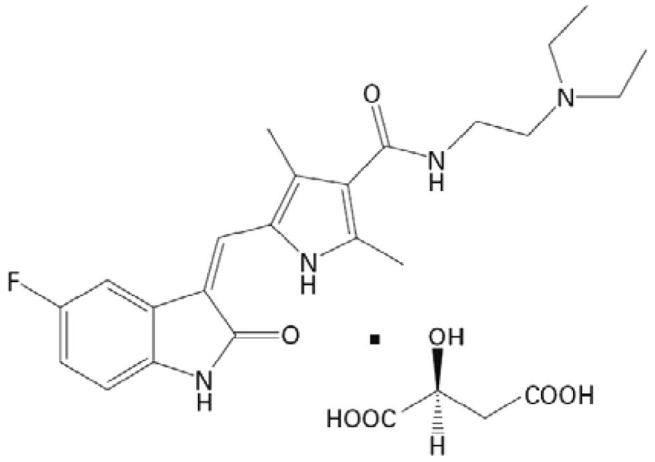

FIGURE 1. Molecular structure of sunitinib.

growth occurred during the rest periods suggested that continuous dosing may be more effective.[9–11] Although both intermittent and continuous dosing strategies are currently being evaluated in ongoing clinical trials, the optimal schedule has not been defined.

SUNITINIB IN NSCLC

The initial phase 2 trial evaluating the role of sunitinib in NSCLC was performed in previously treated patients with advanced NSCLC.[12] The dosage used in the initial trial was 50 mg/d orally for 4 weeks followed by a 2-week rest (4/2 schedule). The eligibility criteria for this trial included only performance status (PS) 0 to 1 patients who had received a platinum-based regimen after which progression was documented. Up to two prior regimens were allowed. Patients were excluded if they had recent gross hemoptysis or evidence of brain metastases. All histologic types of NSCLC were allowed. Sixty-three patients were entered into the trial. The characteristics of the patients were as follows: a median age of 60 years (range, 33–86 years), 65% were male, 44% were PS 0 and 56% were PS 1, 64% had adenocarcinoma whereas 22% had squamous carcinoma, 90% had stage IV disease (10% had stage IIIB), and 16% were never-smokers. The median treatment duration of sunitinib was 11 weeks (range, 1–54 weeks). Twenty-four percent of patients required dose interruption (most commonly due to an adverse event), whereas 22% required a dose reduction. The principal toxic effects observed in this initial cohort included fatigue (27% grade 3–4), pain or myalgia (17% grade 3–4), nausea or vomiting (10% grade 3–4), and hypertension (5% grade 3). Myelosuppression was minimal, with only a 5% rate of either grade 3 to 4 neutropenia or thrombocytopenia. Three hemorrhagic deaths occurred: two pulmonary and one central nervous system. The two pulmonary hemorrhagic deaths were seen in patients with squamous carcinoma, one of which was believed prospectively to be secondary to disease progression. The occurrences of hemorrhagic deaths is similar to the experience with bevacizumab[13,14] and suggest a relationship between antiangiogenic treatment and hemorrhage which may be heightened in patients with squamous histology.

A response rate of 11.1% (95% confidence interval [CI], 4.6–21.6%) was observed, with a stable disease rate of 28.6%. The median time to progression was 12.0 weeks, with a median survival time 23.4 weeks. The 1-year survival rate was 20.2%. The activity observed was similar to the activity of currently approved agents in this patient population, such as docetaxel, pemetrexed, erlotinib, and gefitinib.[15–17]

After this initial experience, it was decided to explore a continuous dosing schedule in the same population given the uncertainty of the optimal schedule of sunitinib. A second cohort of patients (using the identical eligibility and exclusion criteria) was accrued to evaluate a continuous dosing schedule of 37.5 mg/d orally.[14] Since this was a sequential cohort, caution must be exercised with regard to drawing any conclusions from a comparison of these two cohorts. Forty-seven patients were accrued, and the characteristics of these additional patients were essentially identical to the initial cohort of patients accrued to the 4/2 schedule. The median duration of treatment with sunitinib was 92 days (range, 12–336 days). Fifty-one percent required a dose interruption (most commonly due to an adverse event), whereas 29.8% required a dose reduction to 25 mg/d orally. The principal toxic effects included fatigue (17% grade 3–4), dyspnea (8.5% grade 3–4), hemoptysis (2.1% grade 3–4), and hypertension (6.4% grade 3–4). There were no grade 4 hematologic toxic effects; only 9% of patients experienced grade 3 neutropenia, with the remaining hematologic toxic effects being grade 1 to 2. A response rate of 2.1% (95% CI, 0.1–11.1) was observed, with a 19.1% rate of disease stabilization. The median time to progression was 12.3 weeks (95% CI, 8.9–16.0 weeks), and the median survival time was 38.1 week (95% CI, 31.1 week to not available). As noted above, these data cannot be directly compared because the two trials were performed in a sequential fashion. It can be concluded that both doses and schedules showed activity in advanced refractory NSCLC. With regard to toxic effects, both doses and schedules were generally well tolerated, with the overall rate of grade 3 to 4 toxic effects somewhat less with the 37.5 mg continuous dosing schedule. The efficacy results of these two cohorts are summarized in Table 1.

ONGOING TRIALS AND CURRENT ISSUES WITH SUNITINIB IN NSCLC

The data generated by the two trials noted above establish sunitinib as an agent of interest in NSCLC and deserving of further evaluation in this disease. Defining the optimal schedule remains a priority with sunitinib, as is evaluating its role in combination with standard agents or regimens currently used in the treatment of advanced NSCLC. Table 2 summarizes the ongoing sponsored trials evaluating sunitinib in combination with standard agents and regimens in advanced NSCLC. Both intermittent and continuous dosing schedules are being explored. It remains to be seen how easily sunitinib will integrate into the various strategies being explored in the phase 1 trials.

One concern is the toxicity profile of sunitinib as a single agent and, in particular, the observation in the two trials noted above[14,17] that this agent has a low rate of myelosuppression associated with it. This may exacerbate the

TABLE 1. Single-Agent Activity of Sunitinib in Advanced, Refractory NSCLC

	Socinski et al.[12]	Scagliotti et al.[14]
No. of patients	63	47
Dose (mg)	50	37.5
Schedule	4/2*	Continuous
Efficacy		
Partial response (%) (95% CI)	11.1 (4.6–21.6)	2.1 (0.1–11.3)
Stable disease (%)†	28.6	19.1
Median PFS, wk (95% CI)	12.0 (10.0–16.1)	12.3 (8.7–16.0)
MST, wk (95% CI)	23.4 (17.0–28.3)	38.1 (13.1–NA)
1-yr survival (%)	20.2	NA
Toxic effect (grade 3–4) (%)		
Fatigue	29	17
Pain or myalgia	17	2
Nausea or vomiting	10	2
Dyspnea	11	11
Dehydration	8	0

* Four weeks on with a 2-wk rest period.
† For more than 8 wk.
CI indicates confidence interval; MST, mean survival time; NA, not available; NSCLC, non–small cell lung cancer; PFS, progression-free survival.

neutropenia seen with platinum-based regimens similar to the observation with bevacizumab in combination with carboplatin and paclitaxel.[14] This may be less of a concern when adding it to single agents that have low rates of myelosuppression such as pemetrexed.[15] Also, fatigue is a concern because this is a common toxic effect associated with many agents and regimens and a part of the disease process in lung cancer that is often multifactorial. In addition, the use of sunitinib in patients with brain metastases from NSCLC has not been evaluated because these patients were excluded from the trials discussed above. There is an ongoing trial in this population designed to establish the safety of sunitinib in this setting. Likewise, no histologic restrictions were placed on the patients accrued to the single-arm trial noted above, but the issue of safety as it relates to the risk of sunitinib in the squamous cell population needs further definition. As noted, two fatal pulmonary hemorrhages occurred in two patients with squamous cell cancer in the phase 2 trial. Ongoing trials are not excluding patients with squamous cell disease, but this should be carefully evaluated as these trials complete their accrual.

Another issue is how sunitinib should be integrated into the overall treatment plan for patients with advanced NSCLC. This is a complicated question because we currently have three lines of approved agents and regimens, as well as bevacizumab, for treatment choices for our patients. Is the optimal use of sunitinib in combination with standard agents and regimens or as a single agent integrated somewhere into the already complicated treatment approach for these patients? There is not yet adequate data from the phase 1 experience to tell us how well sunitinib combines with other agents and regimens and what dosage is possible with this agent. The one exception is the combination of sunitinib with erlotinib, which appears to be feasible at doses of 37.5 mg/d orally in combination with 150 mg/d orally of erlotinib. This was initially established in the run-in phase of a randomized phase 2 trial, which is currently ongoing. The combination of an anti-EGFR agent in combination with an anti-VEGF agent is attractive, and the preliminary data in NSCLC with the erlotinib/bevacizumab combination are encouraging and provide the rationale for other approaches targeting these pathways. An ongoing phase 3 trial is addressing whether sunitinib in combination with erlotinib will improve survival outcomes in patients with refractory NSCLC.

The Cancer and Leukemia Group B (CALGB) is exploring sunitinib in several unique ways. In CALGB 30607, sunitinib is being evaluated as a maintenance agent compared with placebo (Figure 2). In this trial, patients with advanced-stage IIIB/IV NSCLC who have nonprogressing disease after four cycles of platinum-based chemotherapy with or without bevacizumab will be randomized to 37.5 mg/d orally of either sunitinib or placebo. The primary objective of this trial is prolongation of progression-free survival (PFS), with secondary objectives evaluating overall survival, additional responses as a result of sunitinib, safety and toxicity, and the impact of sunitinib on the time to symptom progression in this population. Although maintenance therapy in NSCLC remains an unproven concept, recent data from a trial of immediate versus delayed docetaxel in the same patient population showed a significant improvement in PFS as a

TABLE 2. Ongoing Clinical Studies of NSCLC

Phase	Description	Sunitinib Dosage	End Point
1	Docetaxel combination	2/1, 25–50 mg	MTD, safety
1	Carboplatin/paclitaxel combination	2/1, 25–50 mg	MTD, safety
1	Gemcitabine/cisplatin combination	2/1, 37.5–50 mg	MTD, safety
2	First-line carboplatin/paclitaxel consolidation therapy	4 cycles of chemotherapy; 4/2, 50 mg to PD	Survival at 1 yr
2	Erlotinib with or without Sunitinib	CD, 37.5 mg	PFS
3	Erlotinib with or without Sunitinib	CD, 37.5 mg	OS
1	Cisplatin/pemetrexed	CD, 37.5–50 mg	MTD, safety
1	Carboplatin/pemetrexed	CD, 37.5–50 mg	MTD, safety
1	Pemetrexed combination	CD, 37.5–50 mg	MTD, safety

CD indicates continuous dosing; MTD, maximum tolerated dose; OS, overall survival; PFS, progression-free survival.

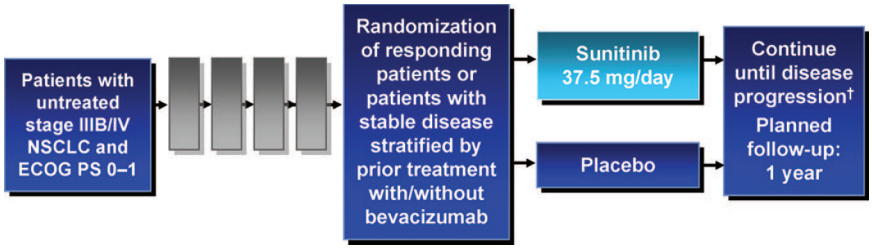

FIGURE 2. Randomized phase 3 trial planned by the Cancer and Leukemia Group B (CALGB) evaluating sunitinib in the maintenance setting in advanced non-small cell lung cancer (NSCLC).

result of immediate or maintenance docetaxel.[19] The use of a well-tolerated, orally administered agent with once-a-day dosing and demonstrated activity in advanced NSCLC seems like a logical candidate to evaluate in such a design and provides the rationale for CALGB 30607.

The observation of the activity of sunitinib, which is similar to other currently approved agents in refractory NSCLC, led to the design of CALGB 30704. This 3-arm randomized phase 2 trial will test sunitinib against pemetrexed versus the combination of sunitinib plus pemetrexed in the second-line setting. Again the primary end point is PFS. This design is of interest because it addresses whether sunitinib compares favorably with the approved cytotoxic standard (pemetrexed) or adds to the efficacy of pemetrexed, which may be the optimal manner in which to use antiangiogenic agents. Lastly, sunitinib is being combined with cisplatin and etoposide in extensive-stage small cell lung cancer in a phase 1/2 design. In the phase 2 portion of this trial, a window-of-opportunity approach is being taken to explore the single-agent activity of sunitinib in previously untreated extensive-stage small cell lung cancer.

POTENTIAL SURROGATE BIOMARKERS

A surrogate end point is an outcome measure that predicts clinical benefit in a selected population. With regard to biomarkers, an outcome may be predicted based on a laboratory or radiologic test and any given biomarker may be helpful for prognostic as well as predictive information. As angiogenesis is a critical and universal process and the role of novel agents directed at the angiogenic process continues to increase, the development of reliable biomarkers is currently an area of intense investigation. Potential candidate biomarkers include soluable forms of pro-angiogenic growth factors including VEGF-A, PIGF, stem cell factor and their receptors as well as circulating endothelial cells and their progenitors (CEPs). In addition, novel vascular imaging techniques such as dynamic contrast-enhanced magnetic resonance imaging, serial positron emission tomography scans and contrast-enhanced ultrasound may also provide important information about the biologic effect of new agents. To date, there has not been sufficient information published on the potential use of these biomarkers in advanced NSCLC with sunitinib. Ongoing studies are currently incorporating the use of putative angiogenic biomarkers in a prospective fashion and hopefully will enlighten this important area of research in NSCLC.[20]

SUMMARY

In conclusion, sunitinib is an active and tolerable agent in advanced NSCLC. Ongoing trials are attempting to integrate sunitinib with standard treatment agents and regimens in advanced NSCLC and SCLC. A better understanding of the mechanism of the fatigue associated with sunitinib should be a priority. Likewise, understanding the mechanism of resistance to sunitinib (both primary and acquired) and determining if sunitinib has any activity in patients previously treated with bevacizumab would help identify the optimal patient for treatment with sunitinib.

REFERENCES

1. Chow LQ, Eckhardt SG. Sunitinib: from rational design to clinical efficacy. *J Clin Oncol* 2007;25:884–896.
2. Arora A, Scholar EM. Role of tyrosine kinase inhibitors in cancer therapy. *J Pharmacol Exp Ther* 2005;315:971–979.
3. Ferrara N, Gerber HP, LeCouter J. The biology of VEGF and its receptors. *Nat Med* 2003;9:669–676.
4. Hanahan D, Weinberg R. The hallmarks of cancer. *Cell* 2000;100:57–70.
5. Sundberg C, Ljungstrom M, Lindmark G, et al. Microvascular pericytes express platelet-derived growth factor-beta receptors in human healing wounds and colorectal adenocarcinoma. *Am J Pathol* 1993;143:1377–1388.
6. Koukourakis MI, Giatromanolaki A, O'Byrne KJ, et al. Platelet-derived endothelial cell growth factor expression correlates with tumour angiogenesis and prognosis in non-small cell lung cancer. *Br J Cancer* 1997;75:477–481.
7. O'Byrne KJ, Koukourakis MI, Giatromanolaki A, et al. Vascular endothelial growth factor, platelet-derived endothelial cell growth factor and angiogenesis in non-small cell lung cancer. *Br J Cancer* 2000;82:1427–1432.
8. Shikada Y, Yonemitsu Y, Koga T, et al. Platelet-derived growth factor-AA is an essential and autocrine regulator of vascular endothelial growth factor expression in non-small cell lung carcinomas. *Cancer Res* 2005;65:7241–7248.
9. Buckstein R, Meyer RM, Seymour L, et al. Phase II testing of sunitinib: the National Cancer Institute of Canada Clinical Trials Group IND program trials IND. 182–185. *Curr Oncol* 2007;14:154–161.
10. Britten CD, Kabbinavar F, Randolph Hecht J, et al. A phase I and pharmacokinetic study of sunitinib administered daily for 2 weeks, followed by a 1-week off period. *Cancer Chemother Pharmacol* 2008;61:515–524.
11. Roskoski R Jr. Sunitinib: a VEGF and PDGF receptor protein kinase and angiogenesis inhibitor. *Biochem Biophys Res Commun* 2007;356:323–328.
12. Socinski MA, Novello S, Brahmer JR, et al. Multicenter, phase II trial of sunitinib in previously treated, advanced non-small-cell lung cancer. *J Clin Oncol* 2008;26:650–656.
13. Johnson DH, Fehrenbacher L, Novotny WF, et al. Randomized phase II trial comparing bevacizumab plus carboplatin and paclitaxel with carboplatin and paclitaxel alone in previously untreated locally advanced or metastatic non-small cell lung cancer. *J Clin Oncol* 2004;22:2184–2191.
14. Sandler A, Gray R, Perry MC, et al. Paclitaxel-carboplatin alone or with bevacizumab for non-small cell lung cancer. *N Engl J Med* 2006;355:2542–2550.
15. Hanna N, Shepherd FA, Fossella FV, et al. Randomized phase III trial of pemetrexed versus docetaxel in patients with non-small cell lung cancer previously treated with chemotherapy. *J Clin Oncol* 2004;22:1589–1597.
16. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al. Erlotinib in

previously treated non-small cell lung cancer. *N Engl J Med* 2005;353: 123–132.
17. Thatcher N, Chang A, Parikh P, et al. Gefitinib plus best supportive care in previously treated patients with refractory advanced non-small cell lung cancer: results from a randomised, placebo-controlled, multicentre study (Iressa Survival Evaluation in Lung Cancer). *Lancet* 2005;366: 1527–1537.
18. Scagliotti G, Novello S, Brahmer J, et al. A phase II study of continuous daily sunitinib dosing in patients with previously-treated advanced non-small cell lung cancer (NSCLC): PD3-3-8. 12th World Conference on Lung Cancer, Seoul, Korea, September 2–6, 2007. *J Thora Oncol* 2007;2(Suppl 4):S470.
19. Fidias P, Dakhil S, Lyss A, et al. Phase III study of immediate versus delayed docetaxel after induction therapy with gemcitabine plus carboplatin in advanced non-small cell lung cancer: Updated report with survival. *J Clin Oncol* (Meeting Abstracts) 2007;25:LBA7516.
20. DePierre A, Milleron B, Moro-Sibilot D, et al. Preoperative chemotherapy followed by surgery compared with surgery in resectable stage I (Except T_1N_0), II, and IIIA non-small cell lung cancer. *J Clin Oncol* 2002;20:247–253.

