

Multi-targeted tyrosine kinase inhibitors for the treatment of non-small cell lung cancer: an era of individualized therapy

Caicun Zhou

Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, Shanghai, China

Corresponding to: Caicun Zhou, MD, PhD. Department of Oncology, Shanghai Pulmonary Hospital, Tongji University School of Medicine, No. 507, Zhengming Rd, Shanghai 200433, China. Email: caicunzhou@yahoo.com.cn.

Abstract: Multi-targeted tyrosine kinase inhibitors (TKIs) have played an increasingly important role in the treatment of non-small cell lung cancer (NSCLC). Many recently published phase III trials have shown bittersweet efficacies of these drugs. How to optimize the efficacies of TKIs has been a hot topic in the era of individualized therapy. In this article, we review the up-to-dated advances in research on the application of TKIs for NSCLC treatment.

Keywords: Lung cancer; multi-targeted drugs; sunitinib; sorafenib; vandetanib; crizotinib



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Introduction

In recent years, the application of targeted drugs has dramatically changed the conventional treatment modes for non-small cell lung cancer (NSCLC). The major milestone events include: in 1962, Cohen *et al.* discovered epidermal growth factor (EGF); in 2008, the iPASS study confirmed the role of epidermal growth factor receptor tyrosine kinase inhibitors (EGFR-TKIs) for advanced EGFR-mutated NSCLC; and in 2010, results from the OPTIMAL trial, for the first time, declared that the median progression-free survival (PFS) of advanced NSCLC patients was prolonged by one year or more after the administration of multi-targeted drug(s) (1,2).

Despite of the scientific carnivals in the past years, however, the efficacies of these drugs for NSCLC were not satisfactory in many clinical trials. For NSCLC patients, these drugs are between a rock and a hard place, although they are theoretically perfect. In this article, we review the up-to-dated research advances on the application of multi-targeted tyrosine kinase inhibitors (TKIs) for NSCLC treatment, with an attempt to summarize evidences for future development.

Anti-tumor mechanisms of multi-targeted TKIs

Multi-targeted TKIs have been regarded as promising for NSCLC due to their unique theoretical bases and anti-tumor mechanisms. First, single-targeted drugs usually have poor efficacies for most NSCLC patients, although they may be

highly effective in certain patients. This can be theoretically explained by the fact that NSCLC is a highly heterogeneous malignancy, with its signal pathways exhibit a complex array of cross connections. As a result, when blocking the key signal transduction pathways, the single-targeted drugs can also activate the tumor escape mechanisms; ultimately, the proliferation of tumor cells may be re-activated via other pathways (3). Obviously, when safety and low-toxicity are guaranteed, drugs should be optimized to inhibit as many as possible of the tumor signal pathways. Second, as shown in *Table 1*, compared with the single-targeted drugs that are targeted at tumor cells only, most multi-targeted drugs can suppress the micro-environment that supports the tumor growth by inhibiting the vascular endothelial growth factor receptor (VEGFR) signal pathway, and thus exert dual anti-angiogenesis and anti-proliferation effects.

Some pre-clinical studies have documented that multi-targeted TKIs can exert their anti-angiogenesis effect by inhibiting the activity of VEGF-dependent vascular endothelial cells. Furthermore, by inhibiting the VEGFR signal pathways, multi-targeted TKIs (e.g., sunitinib) not only degrade tumor microvessels but also inhibit the production of new tumor blood vessels and reduce the effusions of tumor vessels, and ultimately block the blood supply of tumor cells and cause the liquefactive necrosis of tumor cells (4-11).

On the other hand, the direct effects of multi-targeted TKIs on the targets at tumor cell signal pathways can also exert certain anti-

Table 1 IC₅₀ value of different signal pathway by multi-targeted TKIs

Kinase inhibition	Sunitinib (IC ₅₀ , nmol/L)	Motesanib (IC ₅₀ , nmol/L)	Sorafenib (IC ₅₀ , nmol/L)	Vandetanib (IC ₅₀ , nmol/L)
VEGFR-1	2	2	--	1,600
VEGFR-2	4	3	90	40
VEGFR-3	17	6	20	110
PDGFR- α	69	84	--	--
PDGFR- β	39	--	57	1,100
Raf	--	91	6	--
c-Kit	1	8	68	>20,000
FLT3	8	--	58	--
EGFR	>10,000	>3000	>10,000	500
RET	224	59	47	130

proliferative activity against NSCLC. For example, vandetanib can inhibit EGFR signal pathway, sunitinib can inhibit platelet-derived growth factor receptor α (PDGFR α) signal pathway, and sorafenib can inhibit RAS/RAF signal pathway.

Therefore, the multi-targeted drugs with dual actions are superior to single-targeted drugs in terms of action mechanism. Then, how about the real-world clinical data?

Up-to-dated advances in clinical research on multi-targeted TKIs

Sunitinib (Sutent, SU11248)

Sunitinib, chemically known as N-[2-(diemylamino)emyl]-5-[(Z)-(5-fluoro-1, 2-dihydro-2-oxo-3H-indol-3-ylidene)amino]-2, 4-dimethyl-1H-pyrrole-3-carboxamide, is a multi-targeted receptor tyrosine kinase (RTK) inhibitor. Its anti-tumor activities against renal cell carcinoma, gastrointestinal stromal tumors, soft tissue sarcoma, and thyroid cancer have been documented. Since sunitinib has shown good anti-tumor activity in solid tumor cell lines including H226NSCLC (12), many studies have explored its role in fighting against NSCLC. In a phase II trial, Socinski *et al.* (13) demonstrated the anti-tumor activity of sunitinib monotherapy in treating NSCLC patients for whom chemotherapy had failed. In their study, a total of 63 NSCLC patients for whom conventional chemotherapy had failed were enrolled in this study and received 50 mg/d of sunitinib for 4 weeks followed by 2 weeks of no treatment in 6-week treatment cycles. Compared with the baseline level, tumor size shrank by >30% in 15 patients. According to the Response Evaluation Criteria In Solid Tumors (RECIST), seven patients had confirmed partial responses (PR), an additional 18 patients (28.6%) experienced stable disease (SD) of at least 8 weeks in duration. The median duration of sunitinib treatment among patients whose diseases were controlled was 22.1 weeks. Median PFS was 12.0 weeks, and median overall

survival (OS) was 23.4 weeks. The most commonly reported AEs include grade 1-2 and 3-4 fatigue/asthenia (41%/27%), pain/myalgia (43%/17%), and nausea/vomiting (40%/10%). Most AEs were mild to moderate in severity and could be well tolerated. The hematologic toxicities included grade 3 and 4 neutropenia (5%) and thrombocytopenia (5%). For sunitinib, another important issue is the dosing schedule. Therefore, a concurrent phase II trial applied the continuous dosing with 37.5 mg of sunitinib among the same population, and the results are shown in *Table 2*.

Some phase III trials on sunitinib have been initiated based on the results of phase II studies. In 2010, European Society for Medical Oncology (ESMO) formerly released the final results of its randomized double-blind phase III trial (SUN1087). SUN1087 were mainly conducted among NSCLC patients who had failed first-line chemotherapy and sought second-line treatment; by comparing the efficacy of sunitinib plus erlotinib *vs.* sunitinib monotherapy, the study tried to alter the second-line treatment mode for NSCLC through the combined application of targeted drugs. For the general populations, once the first- or second-line platinum-based chemotherapy fails, compared with the sunitinib monotherapy, a combination therapy with sunitinib and erlotinib could significantly prolong the PFS (3.6 *vs.* 2.0 months, $P=0.0023$) and increased the objective response rate ($P=0.0471$) (14). However, due to factors such as subsequent treatment, the OS showed no significant difference (9.0 *vs.* 8.5 months). From the perspective of safety, the adverse effects of the combination therapy were predictable, controllable, and manageable.

Notably, the 2011 World Conference on Lung Cancer released the results of subset analysis of East Asian patients participating in a phase III trial (15). Of 103 Asian patients, sunitinib plus erlotinib remarkably improved the OS of the advanced NSCLC patients: the median OS was unreached (95% CI: 13.4 months-unreached) in the combination therapy

Table 2 50 mg/d 4 weeks on, 2 weeks off vs. 37.5 mg continuous daily dose regimen of sunitinib in NSCLC

		Sunitinib 50 mg/d 4/2 (n=63)	37.5 mg/d CDD (n=47)
Efficacy	ORR (%)	11.1	2.1
	PFS (week)	12.0	12.3
	OS (week)	23.4	37.1
Adverse events (% , grade 1-2/3-4)	Fatigue	41/29	43/17
	Pain	43/17	47/2
	Nausea/Vomiting	43/10	38/2
	Stomatitis	40/3	29/2
	Hypertension	6/5	19/9
	Hemoptysis	NR	15/2
	Neutropenia	44/5	NR/9
	Thrombocytopenia	49/5	NR/0

CDD, continuous daily dose; PFS, progression-free survival; OS, overall survival; ORR, objective response rate; NR, not reported.

group, which was significantly higher than that in sunitinib monotherapy group (9.4 months; 95% CI: 7.5-15.4 months); the hazard ratio (HR) reached 0.532 ($P=0.0101$), and the risk of death decreased by 46.8%. The median PFS in the combination therapy group was 31.2 weeks, versus 15.2 weeks in the monotherapy group ($P=0.0889$). Furthermore, the objective response rate (ORR) in the combination group was almost three times of that in the monotherapy group (38.5% vs. 13.7%). This study had some limitations: it was conducted at the early stage and the drugs were applied as the second-and third-line therapies; meanwhile, it lacked data on the mutations of EGFR gene. Nevertheless, to identify the optimal population through the subgroup analysis in large-scale trials has gradually become a new research direction of targeted drugs. The efficacy of sunitinib in Asian populations deserves further investigation.

Vandetanib (Zactima, ZD6474)

Slightly different from sunitinib, the chemical structure of vandetanib contains anilinoquinazoline, which is currently the most active and selective inhibitor of tyrosine kinase. The main targets of vandetanib include EGFR, VEGFR, and RET. Theoretically, the concurrent inhibition of EGFR and VEGFR, two most important signal pathways for NSCLC, can achieve better clinical efficacy. Interestingly, an earlier phase II trial seemed to prove this theory: in Natale *et al.*'s study, the efficacy and safety of vandetanib was compared with that of gefitinib as the second-line treatment for NSCLC (16). The median PFS was 11.0 weeks for vandetanib and 8.1 weeks for gefitinib ($HR=0.69$, $P=0.025$). OS was not significantly different between patients initially randomized to either vandetanib or gefitinib (median 6.1 and 7.4 months, respectively).

Encouraged by the above phase II trial, three large-scale

phase III trial on the efficacy of vandetanib on NSCLC were concurrently conducted. However, the released results from these trials were striking. The ZODIAC study (17) enrolled 1,400 advanced NSCLC patients to compare the efficacy of vandetanib plus docetaxel with that of docetaxel monotherapy in the second-line treatment of the disease. Although vandetanib prolonged the PFS (median: 4.0 vs. 3.2 months; $HR=0.79$, $P<0.001$), OS was not significantly improved ($HR=0.91$). Furthermore, the results from one study on vandetanib plus pemetrexed (ZEAL) (18) and one study on vandetanib plus erlotinib (19) were even more disappointing: compared with pemetrexed monotherapy or erlotinib monotherapy, either PFS or OS showed no statistically significant improvement although ORR increased to a certain degree. Equally regrettably, the above phase III trials did not carry out stratified analysis on the EGFR gene status and therefore were not able to further identify the potential populations that may benefit from vandetanib. With an IC_{50} of 500 nmol/L against EGFR (20), vandetanib has a low activity in inhibiting EGFR signal pathway, which may also explain why vandetanib failed in the above trials.

Sorafenib (Nexavar, BAY439006)

Sorafenib has highly active aryl urea structure, which has shown high inhibitory effect on RAS/RAF kinase (21). In fact, sorafenib was initially regarded as a serine/threonine kinase inhibitor; further research has found that it can also inhibit the tyrosine kinase in the VEGFR, PDGFR β , and c-Kit signal pathways.

Since bevacizumab had achieved some success in the first-line treatment of NSCLC, two phase III trials were conducted: (I) ESCAPE: sorafenib plus taxol/carboplatin; and (II) NEXUS: sorafenib plus gemcitabine/cisplatin (22,23). Regrettably,

Table 3 Outcome of multi-targeted *vs.* mono-targeted TKIs in NSCLC

Study	Drug	n	Median PFS (week)	Median OS (week)	ORR (%)	DCR (%)
Socinski	Sunitinib	63	11.3	24	9.5	52
Blumenschein	Sorafenib	52	11.9	29	0	59
Ronald B	Vandetanib	83	11	24	8	45
BR21	Erlotinib	488	9.4	28.7	6.9	43.0
Interest	Gefitinib	659	9.4	32.6	9.7	45.8

DCR, disease control rate.

similar to trials on vandetanib, the results of these two trials were unsatisfactory. Furthermore, the mortality of squamous cell carcinoma was remarkably higher in the sorafenib-based combination therapy than in the single chemotherapy group.

In 2010, ESMO released the final results of NEXUS: after 132 patients with squamous cell carcinoma were ruled out, sorafenib combined with gemcitabine/cisplatin still did not improve the patients' ORR and OS (the primary endpoints), which were 28% *vs.* 26% ($P=0.27$) and 379 *vs.* 376 d, respectively. Enrolment stopped in an ongoing MISSION trial (24), which applied sorfenib as the third-and fourth-line therapy for NSCL with an attempt to explore the role of multi-targeted drugs in the third-and fourth-line treatment of NSCLC. Its final results may be interesting.

Other multi-targeted TKIs

Axitinib (AG013736), with VEGFR, PDGFR β , and c-KIT as its main targets, is currently the most potent TKI in inhibiting VEGFR signal pathways (25). Its good anti-tumor activity has been demonstrated in many solid tumors. According to the results of a phase III trial released by ASCO this year, axitinib has become a new standard for the second-line treatment of renal cancer (26). In a phase II study examining the efficacy and safety of axitinib monotherapy in patients with advanced NSCLC, three (3/32, 9.4%) responses were reported, with PFS and OS of 4.9 and 14.8 months, respectively, showing promising anti-tumor activity and safety among NSCLC patients (27,28). Currently, three ongoing phase II studies are exploring the effectiveness and safety of axitinib-based combination therapies (i.e., AGILE1030: axitinib combined with taxol/carboplatin; AGILE1039: axitinib combined with pemetrexed/cisplatin; and AGILE1038: axitinib combined with gemcitabine/cisplatin) in treating non-squamous NSCLC.

Motesanib mainly inhibits targets including VEGFR, PDGFR, KIT, and RET. An early phase Ib trial showed that motesanib plus carboplatin/paclitaxel and/or panitumumab showed good safety for advanced NSCLC. Three dose-limiting toxicities occurred among the 55 patients who had received the combined therapy: grade 4 pulmonary embolism ($n=1$; 50 mg once daily) and grade 3 deep vein thrombosis ($n=2$; 125 mg once daily). The other adverse effects included fatigue, diarrhea,

hypertension, and anorexia. In an ongoing phase III trial, the incidence of hemoptysis increased among squamous NSCLC patients who had been treated with motesanib combined with taxol/carboplatin; as a result, only non-squamous NSCLC patients were included in that study, and the final results require further verification.

Multi-targeted TKIs for NSCLC: Where is the way?

Although multi-targeted TKIs have made certain advances in treating NSCLC, the outcomes remain unsatisfactory if they were applied non-selectively among NSCLC patients. As shown in *Table 3*, among the non-selective populations, TKI monotherapies showed no significant differences when compared with mono-targeted agent monotherapies in treating NSCLC in terms of ORR, PFS, and OS. Therefore, it is extremely important to identify populations that are suitable for TKIs.

First, although lung cancer has some tumor-driven genes, only EGFR mutations and EML4-ALK fusion gene are clinically informative (29), and the role of many other tumor driver genes remain unclear. In patients whose disease is resistant to EGFR-TKIs, particularly, the core oncogenic signal pathways that drive cancer have changed and the tumor is highly dependent on the overlapping signal pathways; as a result, the oncogenic signals exert their oncogenic effects through multiple pathways. Therefore, when the mechanisms governing drug resistance remain unclear, TKIs have certain advantages when applied as salvage treatment after EGFR-TKIs fail. It seems a shortcut for improving the treatment effectiveness by maximizing tumor signal pathway inhibition in the premise of ensuring safety.

The results of the identification of driver mutations in lung cancer specimens, as reported in ASCO and World Conference on Lung Cancer (WCLC) in 2011, also explains the "real world" demand for this choice. The cancer driver genes could not be identified among 46% of adenocarcinoma patients and 37% of squamous cancer patients, even after high-throughput screening technology was applied. For these patients, TKIs may play a more active role. Second, compared with the single-targeted agents, TKIs usually can inhibit more signal pathways; when the key inhibitory signal pathways have not been identified, it is

difficult to decide the targets both practically and theoretically. The targets for anti-angiogenic therapy for NSCLC remain controversial; on the contrary, TKIs usually have dual anti-angiogenic and anti-proliferative effects. Among NSCLC patients showed partial response to the therapy, the dual mode of inhibition often exists; as a result, a hybrid forecasting model with multiple (rather than single) factors can be produced. This issue has to be faced when exploring for the optimal populations of a specific multi-targeted drug. In addition, according to the basic theories of the anti-tumor effects of multi-targeted drugs, for multiple targeted signal pathways, a single drug can not achieve the optimal inhibitory concentrations for all the targets. In other words, when the blood drug levels of a certain drug differ, its inhibitory effects on different targets can also be varied. Such effect also interferes with the homogeneity of the efficacy of a multi-targeted drug among NSCLC patients.

In this regards, the results of SUN1058 trial, which was released in the 2010 annual meeting of American Association for Cancer Research (AACR), may bring some inspiration (30-32). The SUN1058 trial conducted a biomarker analysis in a phase II trial that compared the efficacy of sunitinib plus erlotinib versus erlotinib monotherapy for the second- and third-line treatment of NSCLC. This study basically covered the expressions of all the sunitinib-related targets as well as the mutations of EGFR and KRAS. In this study, the efficacy of sunitinib showed no significant association with the mutations of EGFR and KRAS. In terms of histological indicators, patients with low PDGFR α mRNA expression showed superior response to the treatment than those with high PDGFR α mRNA expression (HR=0.386, P<0.05). Their study also investigated the role of serum protein molecular markers, and for the first time found the correlation between the changes of sVEGFR-3, VEGFC, and sVEGFR-2 and the efficacy of sunitinib. Actually, it is speculated from the SUN1087 trial that only large-scale target screening might make the multi-targeted drugs become more promising for NSCLC.

Conclusions

The efficacy of multi-targeted drugs for NSCLC has not well recognized. For EGFR-TKIs-resistant patients with unknown driving mechanism, the concept of "cancer driver gene" may help to increase the efficacy of multi-targeted drugs for NSCLC (33-35). In other words, individualized treatment based on molecular markers has become a new direction in the treatment of NSCLC. How to choose the right drugs for the right patients and thus achieve the optimal balance between efficacy and adverse effects has become a new research focus in the field of oncology. The future of multi-targeted drugs is highly depended on the capability of delivering these molecule-targeted therapeutics to patients most likely to benefit.

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