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REVIEW ARTICLE

Pazopanib: a new multiple tyrosine kinase inhibitor in the therapy of metastatic renal cell carcinoma and other solid tumors

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Summary

Angiogenesis plays a crucial role in tumor progression. Tumor angiogenesis is driven by host-derived circulating factors. Prominent among these factors is vascular endothelial growth factor (VEGF). Two basic approaches have been pursued in therapies targeting VEGF: neutralization of VEGF by antibodies or inhibition of VEGF receptor (VEGFR). VEGFR inhibition has relied on the use of small-molecular inhibitors. These drugs inhibit the tyrosine kinase activity of VEGFRs as well as other tyrosine kinases, and the term tyrosine kinase inhibitor (TKI) is used to describe this class of drugs. Pazopanib (GW786034), N^4-(2,3-dimethyl-2H-indazol-6-yl]-N^4-methyl-N^2-(4-methyl-3-sulfnonamidophenyl)-2,4-pyrimidinediamine, is a novel orally bioavailable TKI that targets VEGFR1, VEGFR3, platelet-derived growth factor receptor (PDGFR)-alpha, PDGFR-beta and c-kit. Activity was observed in early clinical testing, specifically in patients with metastatic renal cell carcinoma (RCC). In subsequent phase II and phase III trials, the activity of pazopanib was comparable to other targeted agents used in the first-line therapy of metastatic RCC. Promising activity was reported in a number of other tumors, including metastatic carcinoma of the uterine cervix and differentiated carcinomas of the thyroid.

Key words: cervical carcinoma, pazopanib, renal cell carcinoma, tyrosine kinase inhibitors

Introduction

The advent of targeted agents has changed the landscape of medical oncology, resulting in significant improvement of the survival of patients with a wide range of malignant disorders. Targeted agents exert antitumor activity through the inhibition of a defined pathway(s) involved in cancer progression or metastasis, and most agents inhibit tumor growth through more than one mechanism, acting on multiple molecular targets. The progress in the understanding of molecular pathogenesis of cancer progression and metastasis has resulted in the definition of targets for new anticancer agents.

Angiogenesis plays a crucial role in tumor progression. Tumor angiogenesis is driven by host-derived circulating factors [1]. Prominent among these factors is VEGF [2]. VEGF-related family comprises the following proteins: VEGF-A, VEGF-B, VEGF-C, VEGF-D and placental growth factor-1 and -2 [1]. VEGF binds to VEGFR. VEGF-A (often referred to as VEGF), the major cytokine responsible for tumor angiogenesis, binds to VEGFR-2, the most important of VEGF receptors [1,3]. Besides promoting tumor angiogenesis, VEGF may foster tumor growth and progression by causing the phenomenon of tumor hypertension, suppressing immune response, inducing malignant effusions or directly stimulating tumor cell proliferation [4-6]. Two basic approaches have been pursued in therapies targeting VEGF: neutralization of VEGF by antibodies or inhibition of VEGFR by small-molecular weight inhibitors. Bevacizumab, the monoclonal antibody against VEGF is currently used in a wide range of malignant tumors [7-9]. The other approach in the anti-VEGF therapy, VEGFR inhibition, involves the use of small-molecular inhibitors. These drugs inhibit the tyrosine kinase activity of the receptors, and the term TKI is used to describe this class of drugs [3,10]. VEGF binding activates VEGFR. Upon receptor activation, adenosine triphosphate (ATP) binds to specific site of the intracel-

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lular domain of the receptor. Subsequently, phosphate is transferred from ATP to a tyrosine in the VEGFR. Phosphorylation of VEGFR and other proteins transfers the signal downstream [11]. In addition to inhibiting VEGFR tyrosine kinase, these VEGFR TKIs inhibit a range of other tyrosine kinases [12]. The range of TKI inhibition could be of benefit as other tyrosine kinases involved in tumor growth or progression may be inhibited. On the other hand, inhibition of tyrosine kinases could also be responsible for the side effects of therapy.

In general, targeted agents are less toxic and better tolerated than conventional cytotoxic drugs, but a new spectrum of side effects has emerged, including hypertension, hyperlipidemia, impaired glucose tolerance, hypercholesterolemia or skin toxicity. The number of tyrosine kinases inhibited by different TKIs varies widely [12], and, in many instances, the spectrum and severity of side effects increases with increasing number of tyrosine kinases inhibited. Off-target activity, i.e. inhibition of tyrosine kinases that are not involved in tumor growth, could be a problem with TKIs that have a wide range of activity. Thus, the selectivity of TKIs with regard to pathways involved in tumor progression or metastasis is of fundamental importance in drug development.

Preclinical data on the anticancer activity of pazopanib and early clinical trials

Pazopanib (GW786034), N^4-(2,3-dimethyl-2*H*-indazol-6-yl]-N^4-methyl-N^2-(4-methyl-3-sulfnonamidophenyl)-2,4-pyrimidinediamine, is a novel TKI with a favorable selectivity profile. Pazopanib was discovered through complex testing that involved the synthesis of multiple structurally similar compounds [13]. Key points in designing the chemical structure of pazopanib were VEGFR inhibitory activity, pharmacokinetic profile and interaction with cytochrome P450 isozymes. From dozens of synthetic compounds, pazopanib was selected for further development [13]. Pazopanib is an orally bioavailable inhibitor of VEGFR2 that competes at the ATP binding site. Further *in vitro* and *in vivo* investigations revealed that pazopanib had inhibitory activity against a spectrum of additional tyrosine kinases, including VEGFR1, VEGFR3, PDGFR-alpha, PDGFR-beta and c-kit. Inhibitory activity has also been observed against fibroblast growth factor receptor (FGFR)-1, FGFR-2 and c-fms receptor tyrosine kinases. Pazopanib inhibited VEGF and basic fibroblast growth factor induced angiogenesis and the growth of several human tumor xenografts, including colon, prostate, breast and non-small cell lung carcinomas or melanoma, in mice. Steady-state pazopanib concentration of ≥ 40 μmol/L was required for optimal *in vivo* activity [14]. In an *in vitro* study, the kinase selectivity of pazopanib was compared with two other VEGFR TKIs in clinical use, sunitinib and sorafenib, with regard to potential myelosuppression [15]. Among 242 tyrosine kinases studied, pazopanib inhibited at 0.3 μM by more than 50% the activity of 29 kinases, while more than 50% inhibition was observed at the same concentration in 26 kinases for sorafenib and 49 kinases for sunitinib. The concentrations required to induce 50% inhibition of Flt-3 tyrosine kinase were one or two orders of magnitude higher than for sorafenib and sunitinib. Pazopanib and sorafenib exhibited much less inhibition in the hematopoietic progenitor cell colony formation assay compared to sunitinib [15]. Synergistic activity was observed for the combination of pazopanib and lapatinib, a TKI with different spectrum of target kinases [16].

In a phase I study, 63 patients with relapsed or therapy-refractory solid tumors were treated with pazopanib at doses escalating, in cohorts of at least 2 patients, from 50 mg 3 times weekly to 2000 mg daily [17]. Hypertension was the most frequent toxicity observed, but it could be managed by dose modification and/or antihypertensive medications. Other side effects included diarrhea, hair depigmentation, alopecia, skin hypopigmentation, rash, nausea, vomiting, anorexia, dysgeusia, fatigue, visual disturbances, muscle spasms, dizziness, dysphonia, paresthesia and proteinuria. Mild anemia, leukopenia and thrombocytopenia as well as disturbances of electrolyte metabolism, hyperbilirubinemia and mild elevation of transaminases were also observed. Although the maximum-tolerated dose, as defined by the protocol, has not been reached, the dose of 800 mg once daily was selected for further development as pharmacokinetic data indicated that the steady-state exposure to pazopanib may be saturated at doses of 800 to 2000 mg once daily, and in patients treated with higher doses dose reduction was necessary because of fatigue. In this phase I trial pazopanib has showed evidence of clinical activity in patients with refractory malignancies enrolled in the trial, notably in patients with metastatic RCC. Among 12 patients with metastatic RCC enrolled in the trial, partial response was observed in 2 patients and stable disease in 4 [17]. The toxicity profile of pazopanib in the phase I trial compared favorably to other TKIs. Although hyperglycemia has been observed, hypoglycemia was noted as well, and, anecdotally, pazopanib has been reported to improve glycemic control in a cancer patient with type 2 diabetes mellitus [18]. Pazopanib-induced hyperbilirubinemia has been associated with Gilbert's uridine-diphosphoglucuronate glucuronosyltransferase 1A1 polymorphism [19].

Little is known on the predictive biomarkers for

angiogenic agents, including pazopanib, across the spectrum of malignant disorders treated with these agents [20]. In a pioneering study in patients with early stage non-small cell lung cancer several circulating cytokines correlated with tumor response [21]. For baseline cytokine concentrations, the strongest correlation was observed with interleukin-12. During therapy, soluble VEGFR-2 decreased while other cytokines, including placental growth factor, cutaneous T-cell-attracting chemokine, monokine induced by interferon-gamma, and interferon-alpha significantly increased. The decrease of soluble VEGFR-2 and the increase of interleukin-4 correlated with tumor response. These provocative results have obviously to be validated in clinical practice across the spectrum of diagnoses.

Pazopanib in the treatment of metastatic RCC

RCC is resistant to most cytotoxic agents [22]. Just few years ago, the only available therapeutic agents, cytokines, were of questionable activity in most patients with metastatic RCC [23,24]. Because of unsatisfactory results with cytokine therapy in most patients treated, targeted therapies were investigated in metastatic RCC. Two basic therapeutic targets have emerged in this tumor: the VEGF pathway and the mammalian target of rapamycin (mTOR). Recently, targeted agents, including bevacizumab, sorafenib, sunitinib, temsirolimus and everolimus, have shown significant activity, first in patients failing standard (mostly cytokine) therapy, providing second-line treatment in many instances more effective than first-line therapy [25-29]. Currently, targeted agents have replaced cytokines as first-line therapy in metastatic RCC, based on results demonstrating superiority of the combination of bevacizumab and interferon-alpha or sunitinib to interferon-alpha monotherapy [8,30,31]. In addition, the mTOR inhibitor temsirolimus was shown to be superior to interferon-alpha in patients with poor prognosis metastatic RCC [32].

Given the observations of activity of pazopanib in metastatic RCC in early clinical development [17], prospective trials evaluated the efficacy of pazopanib in both pretreated and treatment-naïve patients. The phase II study was originally designed as randomized discontinuation trial, but the design was changed on the recommendation of the data monitoring committee after demonstration of 38% response rate in the first 60 patients [33]. A total of 225 patients were enrolled into the study. About two thirds were treatment-naïve while one third of the patients had prior cytokine- or bevacizumab-based therapy. The final objective response rate was 35%, with no differences in the response rate between treatment-naïve or pretreated patients (34 vs. 37%, respectively). Median progression-free survival (PFS) on pazopanib was 52 weeks [33].

The phase III trial of pazopanib was initiated at the time when no targeted agents were available for the therapy of metastatic RCC. As the only available agents at that time, cytokines, are of questionable benefit for most patients with metastatic RCC [34], comparison with placebo seemed to be justified. A total of 435 patients were randomized at 2:1 ratio between pazopanib and placebo [35]. About half of the patients were cytokine-pretreated while half of the patients were systemic treatment-naïve. The objective response rate in the pazopanib arm was similar in treatment-naïve (32%) and cytokine-pretreated (29%) patients. PFS was significantly prolonged both in the treatment-naïve population (median 11 vs. 3 months) and cytokine-pretreated patients (median 7 vs. 4 months). At the time of analysis, the overall survival (OS) data were immature.

Although the toxicity profile of pazopanib was, in general, favorable in the phase I trial [17], some of the side effects, e.g. hypertension or proteinuria, could represent a specific problem in patients with RCC because of earlier nephrectomy. However, both trials in the RCC patient population confirmed a favorable safety profile of the drug, and grade 3 or 4 side effects were observed in less than 5% of patients [33,35]. As in the phase I trial, hypertension, diarrhea and hair color changes were the most common side effects. Nausea, vomiting, anorexia, fatigue, asthenia, headache, rash, alopecia, hand-foot syndrome, serum transaminase, amylase or lipase increase, hyperglycemia, electrolyte disturbances, anemia, leukopenia or thrombocytopenia were also observed, but these side effects were usually mild. The results of these two trials [33,35] served as basis for regulatory approval of pazopanib in patients with metastatic RCC [36].

Despite the advent of 6 new active agents, the monoclonal antibody bevacizumab, the TKIs sunitinib, sorafenib and pazopanib, and the mTOR inhibitors temsirolimus and everolimus, we still have only a limited number of therapeutic options in patients with metastatic RCC, compared to tumors of other sites. Only very rarely can a patient with metastatic RCC be cured. The optimal management of a patient with metastatic RCC should therefore strive to maximally utilize the potential of all active therapeutic agents [37]. Currently we have 3 options demonstrating therapeutic benefit in the first-line therapy, i.e. the combination of bevacizumab and interferon-alpha, or the TKIs sunitinib and pazopanib. The activity of all these 3 therapeutic options in randomized clinical studies, whether assessed by response rate or PFS duration, is comparable. As the efficacy of these

therapies appears to be comparable, the spectrum of side effects plays an important role in the choice of treatment. Because of similarity of the effectiveness of bevacizumab with interferon-alpha, sunitinib or pazopanib, it seems likely that the antitumor activity of all these therapeutic agents is mediated through inhibition of VEGF signaling. Off-target activity of the drugs may limit the usefulness in this setting because it may cause toxicity. Bevacizumab is the most specific of these targeted agents, and has no off-target activity. However, bevacizumab is administered in combination with interferon-alpha, and interferon-alpha is responsible for a significant proportion of toxicity of the combination [38]. Off-target tyrosine kinase inhibition is clearly responsible for many side effects of sunitinib. These side effects impair the quality of the life of the patients, and may necessitate dose interruptions or reduction that could result in impaired efficacy. The efficacy of pazopanib appears to be comparable with sunitinib, but the drug seems to be better tolerated, specifically during prolonged therapy. Unfortunately, no data on direct head-to-head comparison of targeted agents in the first-line therapy of metastatic RCC are currently available, and all comparisons outlined above are indirect and conclusions have to be drawn with caution. The choice of the first-line therapy should be based on the discussion with the patients. Important issues affecting the patient preference could be the mode of administration (oral agents vs. subcutaneous and intravenous administration), cost of the drugs or expenses associated with the therapy.

The choice of second-line therapy in metastatic RCC is even less clear [37]. The data on the choice of second-line therapy of patients failing cytokines are now mostly only of historical interest. For the current standard of care of first-line therapy of metastatic RCC targeted agents, the only phase III data are available for everolimus in patients failing sunitinib or sorafenib or both agents [29], and for other situations, most data on the activity of second-line therapy are based on retrospective series. Data on the activity of pazopanib in patients failing other targeted agents or on the activity of other targeted drugs in patients failing pazopanib are currently virtually non-existent. The phase II trial of pazopanib that demonstrated similar efficacy in treatment-naïve and pretreated patients included only 10 patients previously treated with bevacizumab, but no details are available on pazopanib activity in this particular subgroup [33].

Activity of pazopanib in other tumors

Besides metastatic RCC, activity of pazopanib has been demonstrated in a number of solid tumors, including carcinoma of the uterine cervix, ovarian cancer, breast cancer, non-small-cell lung cancer, glioblastoma, thyroid cancer, or soft-tissue sarcomas. Clinical trials are currently underway in patients with other malignant neoplasms.

So far, the most promising results on pazopanib activity were reported in patients with metastatic carcinoma of the uterine cervix. In a randomized phase II trial, 228 patients with advanced or recurrent cervical cancer who had at least one prior chemotherapy regimen were randomized between the therapy with pazopanib, lapatinib or the combination of pazopanib and lapatinib [39]. Objective response was observed in 9% of patients treated with pazopanib and 5% of patients treated with lapatinib. PFS and OS were significantly prolonged in patients treated with pazopanib (18 vs. 17 weeks and 51 vs. 39 weeks, respectively) [39].

Promising activity was also observed in patients with recurrent ovarian cancer. In a phase II study, 36 patients with recurrent ovarian cancer who had received one or two lines of prior chemotherapy that included first-line platinum-based regimen received pazopanib at the standard dose of 800 mg once daily [40]. The response rate based on CA-125 levels was 31%. PFS at 6 months was 17% [40].

In a phase II trial, pazopanib was administered to 20 patients with breast cancer that had progressed after one or two lines of chemotherapy [41]. One patient had partial response and 11 (55%) stable disease as their best response. Median PFS was 5 months and median OS 13 months. In a proof-of-concept study, the activity of pazopanib was assessed in patients with stage I or II non-small-cell lung cancer scheduled for curative surgery [42]. Thirty-five patients, predominantly with stage I disease, were enrolled and 30 patients (86%) were treated with pazopanib for 2 weeks or longer. Most patients (86%) had some tumor-volume reduction, and partial response was observed in 3 cases [42].

Pazopanib activity was also investigated in less common malignancies, including glioblastoma, thyroid cancer and soft tissue sarcomas. There is increasing evidence indicating that anti-VEGF therapy is active in patients with glioblastoma. In a phase II trial, 35 patients with glioblastoma progressive after radiotherapy and 1 to 3 lines of chemotherapy were treated with pazopanib (800 mg once daily) [43]. Two patients had partial response, median PFS was 12 weeks, only one patient was progression-free after 6 months and median OS was 35 weeks [43]. Radioiodine-refractory differentiated thyroid cancer represents an essentially orphan disease, with few standard therapeutic options available. Among 37 patients with radioiodine-refractory differen-

tiated thyroid cancer (papillary, follicular or Hürthle cell carcinomas) treated with pazopanib in a phase II trial, partial response was observed in 18 cases (49%) [44]. More responses were seen in patients with follicular carcinoma (73%) than with Hürthle cell carcinoma (45%) or papillary carcinoma (33%), but, because of the limited number of patients enrolled, these differences were not statistically significant. PFS and OS at 1 year were 47 and 81%, respectively, and it has been estimated that the response would last longer than one year in two thirds of the patients [44]. Anecdotally, response to pazopanib has also been described in a patient with metastatic Merkel cell carcinoma, a rare skin malignancy [45].

Soft tissue sarcomas are a very heterogeneous group of malignant disorders. Because of rarity of these tumors, most clinical trials have included patients with a range of histologies. However, the differences in biology, clinical behavior or sensitivity to anticancer agents among different soft tissue sarcomas are comparable to the differences observed among epithelial carcinomas of different primary location. It is therefore not surprising that the results of drug trials that included different soft tissue sarcomas were either inconsistent or outright negative. Anti-VEGF therapy targets a mechanism of tumor progression common in different neoplasms. Therefore, anti-VEGF drugs like pazopanib could be active in soft tissue sarcomas of different histology. To test this hypothesis, 142 soft tissue sarcoma patients were enrolled in a prospective trial [46]. To evaluate the efficacy of pazopanib, the patients were grouped into 4 strata: adipocytic soft tissue sarcoma, leiomyosarcoma, synovial sarcoma and other soft tissue sarcoma. The primary endpoint of the study was PFS at 12 weeks. The primary end point of efficacy was not met in patients with adipocytic soft tissue sarcoma (12-week PFS 26%). PFS at 12 weeks in the other strata was higher (leiomyosarcoma 44%, synovial sarcoma 49% and other soft tissue sarcomas 39%). Partial responses were observed in 9 patients, one patient with leiomyosarcoma, 5 patients with synovial sarcomas and 3 patients with other soft tissue sarcomas.

Potential of future development of pazopanib

Potential directions of future development of pazopanib include the use of this drug as adjuvant therapy after surgery in patients without evidence of distant metastases, e.g. in RCC, its combination with cytotoxic agents or the use of this agent in new indications.

Currently, there is no effective adjuvant therapy in patients with non-metastatic RCC. However, the recurrence rate after nephrectomy in certain subgroups of patients is relatively high, and availability of agents that would prolong recurrence-free survival and increase the cure rate in this population is an unmet medical need. Given the mechanism of action of targeted drugs that are active in RCC, therapy would probably have to be prolonged. Thus, the issue of toxicity of adjuvant therapy will be very important. Because of the activity of pazopanib in metastatic RCC and its favorable toxicity profile, this drug represents a good candidate for adjuvant therapy to be tested in randomized prospective clinical trials.

In a phase I study pazopanib was combined with weekly paclitaxel [47]. Maximum tolerated doses were 800 mg once daily for pazopanib and 80 mg/m^2 for paclitaxel. Partial response was observed in 5 out of 17 patients treated with the maximum tolerated doses of both agents. All these responding patients had previous taxane therapy [47].

There are preclinical data indicating activity of pazopanib in hematological malignancies, e.g. chronic lymphocytic leukemia and multiple myeloma [48,49]. It remains to be determined whether pazopanib will also be useful in the clinic in patients with these neoplastic disorders.

Conclusions

Pazopanib is a new TKI targeting VEGFR-1, VEGFR-2, VEGFR-3, PDGFR-alpha, PDGFR-beta and c-kit with a favorable toxicity profile. While pazopanib is currently registered only for the therapy of metastatic RCC, it has promising activity in a number of other tumors, including metastatic carcinoma of the uterine cervix and differentiated carcinomas of the thyroid.

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