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MET and VEGF: synergistic targets in castration-resistant prostate cancer

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Abstract

Recent advances in the treatment of prostate cancer have resulted in improved outcomes, including longer survival, but new options are needed for treating patients with castration-resistant disease, particularly in the presence of bone metastasis. Data from preclinical models and clinical biomarker studies indicate that antiangiogenic agents should be a promising treatment for this patient population, and multiple agents in this class have demonstrated activity in early-stage clinical trials. Pivotal trials in prostate cancer with agents targeting vascular endothelial growth factor (VEGF) signalling have resulted in significant improvements in tumour response and progression-free survival. However, overall survival was not significantly improved. Recent preclinical studies suggest that the limited impact on overall survival may result from the development of evasive resistance after inhibition of angiogenesis, possibly through upregulation of MET (hepatocyte growth factor receptor) signalling. MET plays important roles in angiogenesis, tumour cell invasion and bone metastasis, all of which are key factors in castration-resistant prostate cancer. Inhibition of both the MET and VEGF pathways may improve the efficacy of angiogenesis inhibitors in prostate cancer.

Keywords

Angiogenesis inhibitors; c-met proteins; Prostate cancer; Neoplasm invasiveness; Metastasis

Introduction

Prostate cancer is the most common non-cutaneous cancer in men. In 2010, an estimated 217,730 new prostate cancer cases were diagnosed in the USA, and more than 32,000 deaths were estimated to occur, making it the second-leading cause of cancer-related death in men [1]. As prostate cancer cells express androgen receptors and are initially androgen-dependent, hormonal-based therapy–also referred to as androgen deprivation therapy–is the

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Conflict of interest

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initial treatment of choice [2]. While the disease typically responds to this therapy, nearly all patients eventually progress despite castrate levels of androgens (<50 ng/ml); at this stage the disease is known as castration-resistant prostate cancer (CRPC) [2]. Early clinical manifestations of progressive CRPC include bone metastases, rising serum prostate-specific antigen (PSA) levels and pain [3]. Multiple drugs have been approved for CRPC, including the chemotherapeutics docetaxel and cabazitaxel, the immunotherapeutic sipuleucel-T, and the androgen biosynthesis inhibitor abiraterone [4]. While these agents can prolong survival, the prognosis for CRPC remains poor and new therapeutic approaches are needed.

Antiangiogenic therapy in prostate cancer

Angiogenesis is essential for tumour growth and metastasis [5–7]. Antiangiogenic approaches, most of which rely on targeting the vascular endothelial growth factor (VEGF) signalling pathway, have emerged as important therapeutic options in treating a range of cancers, including those of the lung, colon, breast and kidney. VEGF-driven angiogenesis also appears to be a promising target in prostate cancer. Expression of VEGF is low in normal prostate tissues [8] but is upregulated in metastatic prostate cancer [8, 9]. In addition, the microvascular density of prostate tumours correlates with disease progression [10, 11], and elevated levels of VEGF in plasma or urine correlate with advanced stage, progression and poor patient outcomes in prostate cancer [9, 12, 13].

Based on these findings, and on promising treatment responses in other tumour types, multiple antiangiogenic agents that target VEGF signalling have been studied in patients with CRPC. Improvement in tumour response and/or progression-free survival was observed with bevacizumab, sorafenib, sunitinib and cediranib in phase 2 trials in CRPC [14–20]. Similar benefits were observed with bevacizumab and sunitinib in phase 3 trials [21, 22]. However, statistically significant improvement in overall survival was not found in the latter pivotal trials.

Similar results were obtained with several antiangiogenic agents in a variety of tumour types other than CRPC, where evidence of initial clinical benefit, such as tumour response and delayed progression, was not accompanied by improved overall survival in pivotal trials [23, 24]. Additionally, while agents that target the VEGF signalling pathway have been clinically important in treating some tumour types, their efficacy in many patients is transient and eventually followed by tumour growth and progression [25–27]. In glioblastoma, relapse in some patients was associated with a concerning increase in tumour invasion and multifocal spread within the brain [28, 29]. These clinical outcomes suggest that the failure to achieve enduring clinical benefit with treatment in some trials may result from the development of resistance to antiangiogenic therapy.

Rationale for targeting MET

Experiments in mice have demonstrated that tumours are capable of developing adaptive or evasive resistance to therapies targeting the VEGF signalling pathway [23, 30, 31]. This response of tumours to therapy is characterised by a more highly invasive and metastatic phenotype, and has been described with a wide variety of agents including the small molecule tyrosine kinase inhibitors (TKIs) sunitinib, sorafenib and cediranib, antibodies that

recognise and neutralise VEGF (including bevacizumab), and a VEGFR2-targeting antibody [28–30, 32–35]. One potential mechanism for the development of evasive resistance to VEGF-pathway inhibition is upregulation of MET pathway signalling [36].

MET, the receptor for hepatocyte growth factor (HGF), is a receptor tyrosine kinase that plays important roles in cell motility, proliferation and survival, and is a key factor in tumour angiogenesis, invasiveness and metastasis [37–39]. Both MET mRNA and protein levels are substantially increased by hypoxia, which can increase cell invasion and migration away from hypoxic regions after treatment with an angiogenesis inhibitor [35, 40, 41].

Expression of HGF is increased in murine tumour models resistant to sunitinib, and systemic administration of HGF can cause resistance to sunitinib in models that are otherwise sensitive to sunitinib [42]. Likewise, combined therapy with sunitinib and a selective inhibitor of MET is significantly more efficacious than therapy with either agent alone in sunitinib-resistant murine tumour models [42]. In addition, TKIs such as cabozantinib (XL184) and foretinib (XL880; GSK1363089), which simultaneously target the MET and VEGF signalling pathways, have a profound impact on tumour vasculature and block the development of tumour invasiveness and metastasis [35, 36]. These results are consistent with a contribution of MET signalling to the development of resistance to VEGF inhibition.

In prostate cancer, growing evidence suggests that MET signalling may play an important role in promoting malignancy, even in the absence of VEGF pathway inhibition. Expression of MET is high in benign prostate tissue (largely in basal cells) and in primary and metastatic prostate carcinomas [43–46]. MET expression is higher in bone metastases than in primary tumours or lymph node metastases [47, 48]. Expression of HGF is greater in prostate carcinoma than in benign prostate tissue [11, 13], and high plasma levels of HGF in men with CRPC correlate with decreased overall survival [49].

Data from preclinical and clinical studies suggest that HGF and MET are regulated by androgen signalling in prostatic cells. HGF expression is low in androgen-sensitive CWR22 xenograft tumours and is significantly up-regulated in castration-resistant variants [50]. Similarly, androgen-sensitive prostate cancer cell lines grown in the presence of androgen typically express low or undetectable levels of MET, while CRPC cell lines generally express higher levels [46, 51]. MET expression increases substantially in androgen-sensitive cells after androgen withdrawal in vitro or after castration in androgen-sensitive xenograft tumours growing in vivo [46, 51, 52]. A similar effect has been described in normal rat prostate tissue after castration [46].

These preclinical findings are consistent with clinical observations that MET expression is significantly greater in tumour samples from patients with CRPC than in specimens from patients who have not yet undergone androgen deprivation therapy [53]. A possible mechanism for this difference is evident in molecular studies showing that the androgen receptor directly represses expression of the gene encoding MET via inhibition of its promoter [51]. Overall, these observations indicate that MET expression is particularly high in prostate cancer bone metastases and that increased MET signalling may reflect the emergence of castration-resistant disease.

Roles for MET and VEGF signalling in bone metastases

The primary cause of morbidity and mortality in patients with CRPC is metastasis to bone, which occurs in about 90% of cases [3, 54]. Bone metastasis is a complex process involving interactions between the cancer cells and components of the bone microenvironment including osteoblasts, osteoclasts and endothelial cells [54]. Bone metastases cause local disruption of normal bone remodelling, with lesions generally exhibiting a propensity for either osteoblastic (bone-forming) or osteolytic (bone-resorbing) activity. Although most CRPC patients with bone metastases have features of both types of lesions, prostate cancer bone metastases are generally characterised as predominantly osteoblastic, with abnormal deposition of unstructured bone accompanied by increased skeletal fractures, spinal cord compression and severe bone pain [54, 55].

Osteoblastic lesions are typically visualised in CRPC patients by bone scan, which detects rapid incorporation of ^{99m}Tc-labelled methylene-diphosphonate (^{99}Tc-MDP) radiotracer into newly forming or remodelling bone. Increased levels of bone-specific serum alkaline phosphatase, a marker for osteoblast activity, are often observed in CR-PC patients with bone metastases and are associated with shorter overall survival [55].

MET signalling can influence osteoblast and osteoclast function. Strong immunohistochemical staining of MET has been observed in osteoblasts in developing bone [56], while both HGF and MET are expressed by osteoblasts and osteoclasts *in vitro* and regulate cellular responses such as proliferation, migration and differentiation [57–60]. Secretion of HGF by osteoblasts has been proposed as a key factor in osteoblast/osteoclast coupling [58] and is thought to promote the development of bone metastases by tumour cells that express MET [61].

Like MET, the VEGF signalling pathway is strongly implicated in bone formation and remodelling. Both osteoblasts and osteoclasts express VEGF and VEGF receptors, which appear to be involved in autocrine and/or paracrine feedback mechanisms regulating cell proliferation, migration, differentiation and survival [62–66]. Experiments using genetically modified mice have shown that angiogenesis and VEGF signalling in osteoblasts are both important in bone development and repair [67, 68].

Clinical studies with inhibitors of MET signalling in CRPC

Based on the preclinical and clinical findings described above, in the treatment of CRPC there is a clear rationale for inhibition of the MET signalling pathway, either alone or with inhibition of the VEGF pathway. However, very few MET-targeted agents have been studied in this setting (Table 1). A recently completed phase 1 clinical trial studied the safety and tolerability of the selective MET inhibitor tivantinib (ARQ 197) in patients with solid tumours, including 13 patients with CRPC [69]. Phosphorylated and total MET protein in tumour biopsies and number of circulating tumour cells (CTCs) were reduced in some patients after tivantinib treatment. However, objective RECIST tumour responses or PSA responses were not found in this trial and no changes in bone lesions were reported. In a separate phase 1 trial with tivantinib, a partial response was observed in one CRPC patient [70].

Interim results from a phase 2 randomised discontinuation trial of the MET/VEGFR inhibitor cabozantinib in patients with CRPC showed encouraging clinical activity [71]. Regression of soft tissue/visceral lesions was found in 74% of patients and 10 patients met RECIST criteria for a partial response. A subset of patients with stable disease as their best response after the initial 12 weeks of treatment was randomised to receive either cabozantinib or placebo. The cabozantinib-treated group had significant improvement in progression-free survival. Despite substantial activity against soft tissue/visceral lesions, consistent effects on PSA were not observed and PSA was increased in some patients who had signs of clinical benefit [72].

The most intriguing findings in this trial came from the ^{99}Tc-MDP bone scans of patients with bone metastases. Complete or partial resolution of lesions visible in bone scans was found in 82% of patients treated with cabozantinib; this improvement was often accompanied by pain relief and reduction in narcotics usage. Reductions in blood-based markers of osteoblast and osteoclast activities were also observed, consistent with diminished activation of these cells in patients with bone lesions. Whether these effects will ultimately translate into improved overall survival will need to be assessed in future clinical trials. Based on the high incidence of improvement in patients with bone lesions, a subsequent phase 1 study was initiated in patients with CRPC to determine the tolerability and activity of lower starting doses of cabozantinib (Table 1).

An ongoing phase 1b/2 trial is evaluating the safety and efficacy of rilotumumab (AMG 102), a monoclonal antibody that blocks the action of HGF, in combination with mitoxantrone and prednisone in patients with previously treated CR-PC [73]. Results have not yet been reported for this study; however, in April 2011 the sponsor announced that development of rilotumumab would be discontinued [74].

Beyond PSA: assessing treatment response to antiangiogenic TKIs in CRPC

Many trials evaluating antiangiogenic agents in prostate cancer have used PSA measurements to assess disease response and progression. Serum PSA is easily and reproducibly measured, and decreased PSA in prostate cancer patients correlates with better overall survival during treatment with androgen deprivation and chemotherapy [75–77]. However, conflicting or confounding changes in serum PSA have been found after treatment of CRPC with antiangiogenic TKIs (Table 2). Few patients in trials with cediranib, sorafenib, sunitinib and cabozantinib had declines in PSA despite reductions in pain and lymph node, lung, liver and/or bone lesions [16–20, 71, 72, 78, 79]. In some patients with objective tumour regression and reduced pain, PSA levels increased substantially during treatment and then decreased after discontinuation of treatment [16, 20, 79].

In vitro experiments have shown that PSA secretion from prostate cancer cells can increase during incubation with sorafenib [16] and PSA expression in prostate cancer cells can decrease in the presence of osteoblasts [80]. These results suggest that during treatment of CRPC patients with angiogenesis inhibitors, changes in serum PSA may reflect a pharmacodynamic effect of tyrosine kinase inhibition in tumour cells or changes in osteoblast–tumour cell interactions in bone lesions, rather than changes in tumour growth.

In light of these and other observations, the Prostate Cancer Clinical Trials Working Group has emphasised the importance of radiographic or symptomatic progression over PSA progression in trials of antiangiogenic agents, and recommended against discontinuation of therapy solely on the basis of serum PSA changes [3]. These recommendations indicate the need to develop and validate criteria other than PSA progression for assessing treatment effects.

As bone is the most common site of metastasis in prostate cancer, evaluating treatment effects on bone lesions has potential as a useful measure of the therapeutic efficacy of antiangiogenic agents. Changes in bone scan measurements may be more predictive of survival than changes in PSA levels [81, 82]. However, changes in bone metastases are typically difficult to measure objectively and reproducibly by bone scan [83, 84]. New techniques are being developed for computer-assisted detection and assessment of bone lesions that would greatly improve their utility as a standardised measure of treatment effects [85, 86].

CTCs are another promising measure of angiogenesis inhibitor effects in prostate cancer. CTCs have been shown to have prognostic value in CRPC [87, 88]. Lower CTC counts correlate with better overall survival for patients treated with cytotoxic chemotherapy or targeted therapies [89–92]. However, additional clinical trials are needed to validate the use of CTCs as a surrogate endpoint and more robust technologies are needed to improve the detection of CTCs [93].

Conclusions

Ongoing clinical trials of inhibitors of VEGF signalling in CRPC have shown promising results, but thus far no over-all survival benefit has been found. The lack of survival benefit may reflect the development of evasive resistance during treatment. Upregulation of MET signalling in tumours is a potential mechanism of this resistance. Preclinical and clinical results indicate that targeting of MET and VEGF signalling together has advantages over targeting either pathway alone. The benefit of simultaneous inhibition of MET and VEGFR is evident in the resolution of bone lesions visible in bone scans of many CRPC patients treated with cabozantinib, which blocks both pathways. The evaluation of clinical benefit in trials of angiogenesis inhibitors in CRPC is confounded by rising PSA levels in some patients, despite evidence of clinical benefit and/or lack of tumour progression. Clinical and preclinical data suggest that rising PSA may be a consequence of antiangiogenic TKI therapy and may not be useful for assessing the efficacy of these agents in CRPC. Other measures of treatment efficacy, such as bone scans or CTCs, may be more meaningful in future clinical trials for assessment of agents that target MET and VEGF signalling pathways in CRPC.

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Table 1

Key trials examining MET inhibition in CRPC

Study	Tumour type	Endpoints	Results	ClinicalTrials.gov identifier/reference
Tivantinib, phase 1	Advanced solid tumours (N=51); CRPC cohort (n=13)	Safety PK/PD assessments Preliminary antitumour activity	Observed decreases in phosphorylated and total MET levels Declines in CTCs and circulating endothelial cells No tumour responses observed	NCT00612209, Yap et al (2011) [69]
Tivantinib, phase 1	Advanced solid tumours	Safety PK/PD assessments Preliminary antitumour activity	Partial response observed in one CRPC patient	NCT00302172, Mekhail et al (2009) [70]
Cabozantinib, phase 2	Advanced solid tumours (N=490); CRPC cohort (n=171)	ORR, PFS Safety PK/PD assessment	In the CRPC cohort, interim results reported significant disease control rates (partial response +stable disease) Reduction or stabilisation of metastatic bone lesions was observed in nearly all evaluable patients	NCT00940225, Hussain et al (2011) [71]
Cabozantinib, phase 1	CRPC	Changes in bone scans, bone biomarkers, and CTCs	Trial is currently recruiting patients	NCT01347788
Rilotumumab+ mitoxantrone+ prednisone, phase 1b/2	CRPC	OS, PFS Safety PK/PD assessment PSA response rate	Trial is ongoing, but no longer recruiting patients	NCT00770848

ORR, objective response rate; PFS, progression-free survival; PK, pharmacokinetic; PD, pharmacodynamic; OS, overall survival

Table 2

PSA and clinical results with antiangiogenic TKIs in CRPC

Study	PSA results	Clinical results	Reference
Cediranib, phase 1 CRPC (N=26)	No PSA declines ≥50% during protocol therapy 4 patients with PSA reductions within 30 days after study drug discontinuation, 3 of whom had seen PSA rises while on study therapy Post-therapy PSA declines lasted >17 months in 2 patients despite PSA increases while on therapy	28.6% of patients with best response of SD by RECIST 1 patient with resolution of retroperitoneal adenopathy; exhibited 93% PSA decline after study drug discontinuation	Ryan et al (2007) [20]
Cediranib, phase 2 CRPC (N=53)	PSA levels increased dramatically in some patients with tumour responses	55.9% of patients with evaluable disease had tumour shrinkage 17.6% of patients with best response of PR by RECIST Decreases in metastases in lymph nodes, lung, liver and bone	Adelberg et al (2010) [17]
Cabozantinib, phase 2 with mCRPC cohort (N=171)	PSA changes not correlated with other efficacy parameters	68% disease control rate (PR+SD) at week 12 74% of patients had measurable disease regression Pain improvement in 67% of patients with pain at baseline 82% of patients had complete or partial resolution of lesions on bone scan	Smith et al (2011) [72] Hussain et al (2011) [71]
Sorafenib, phase 2 mCRPC in two stages (n=22 and n=24)	No PSA response in either stage; in stage 1, 61.9% of patients progressed only by PSA criteria in the absence of clinical and radiographic progression	In stage 1, 2 patients showed regression in bone lesions despite meeting PSA progression criteria at the time; 18.2% of patients had progressive bone disease In stage 2, 7.7% of patients had PR by RECIST, 41.7% had SD (assessed by clinical or radiographic data)	Aragon-Ching et al (2009) [78]
Sorafenib, phase 2 chemotherapy-naive CRPC (N=57)	20% of patients had SD by PSA, 3.6% had PSA responses, 38.1% had PSA progression	7.3% of patients had SD by RECIST 8 weeks median PFS, 13% 1-year PFS rate (progression by PSA or RECIST) Estimated 68% 1-year OS rate	Steinbild et al (2007) [15]
Sunitinib, phase 2 CRPC (N=34)	PSA response (≥50% decline) was the primary end point: 5.8% of patients had PSA responses, 44.1% had stable PSA at week 12 Improvements in clinical symptoms, pain, CT scan and/or bone scan observed in patients with rising PSA values	3.3% of patients had PR by RECIST, 60% had SD 3 patients showed improvement in bone scan	Michaelson et al (2009) [18]
Sunitinib, phase 2 docetaxel pretreated mCRPC (N=36)	12.1% of patients had PSA responses Discordant PSA increases seen in 45.5% of patients with improvements in pain scores	11.1% of patients had ≥30% declines by RECIST; 44.4% had some tumour shrinkage Decline in pain score ≥2 points in 13.6% of patients, ≥1 point in 50%	Sonpavde et al (2010) [19]

(m)CRPC, (metastatic) castration-resistant prostate cancer; SD, stable disease; PR, partial response; PFS, progression-free survival; RECIST, Response Evaluation Criteria in Solid Tumours; OS, overall survival; CT, computed tomography