REVIEW

The role of vascular endothelial growth factor in kidney and prostate cancer

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Background: *Vascular endothelial growth factor (VEGF) is a key regulator of physiological angiogenesis, but has also been implicated in pathological angiogenesis associated with renal cell carcinoma (RCC) and prostate cancer (PCa).*

Material and methods: *This review of literature underlines the recent advances in the understanding of how VEGF acts through these two malignancies, its potential value as a diagnostic and prognostic marker, as well as the development of new therapeutic strategies targeting the VEGF pathway.*

Results: *In RCC, VHL gene inactivation mediates over-expression of VEGF. Multiple approaches to block VEGF signaling in kidney cancer have been tested. VEGFR-specific small molecule tyrosine kinase inhibitors (TKIs), multikinase inhibitors (MKI) and monoclonal antibodies (Mabs) against VEGF have been evaluated in patients with RCC in phase II-III trials. The development of these new treatment strategies led to the attempt to identify predictive markers of treatment benefit. However, no true marker has been yet identified. In PCa, VEGF expression is regulated by androgens, and recent studies suggest a correlation between angiogenesis and biological aggressiveness. Some authors have investigated the value of VEGF as a screening test for PCa, as a tool for PCa staging, and as a target for therapeutic strategies.*

Conclusions: *The understanding of the VEGF pathway and the development of angiogenesis-directed therapies have had a major impact on the treatment of metastatic RCC. In PCa, the usefulness of VEGF as a prognostic factor is highly suggested, but remains to be clarified. In addition, anti-angiogenic treatments targeting the VEGF pathway are currently under investigation.*

Key Words: vascular endothelial growth factor, prostate cancer, kidney cancer, angiogenesis

Introduction

The growth of many solid tumors depends on angiogenesis. Therefore, proangiogenic proteins have become a large field of investigation and a promising area for new therapeutics. Vascular endothelial growth factor (VEGF) is one of the most potent and well-characterized proangiogenic proteins. The VEGF gene expression is activated by the transcription complex hypoxia inducible factor (HIF) in response to changes in oxygen tension. The induction of VEGF expression in hypoxic tissues results in enhanced blood flow.[1,2]

VEGF is the most prominent cytokine responsible for endothelial cell differentiation, migration, proliferation, tube formation and vessel assembly.[3] Thus, VEGF stimulates angiogenesis, but has also many other functions. Produced by a wide variety of cell types, there are five different isoforms of VEGF that are generated by alternate splicing of a single gene: VEGF-A, VEGF-B, VEGF-C, VEGF-D and VEGF-E. There are three VEGF tyrosine kinase receptors: VEGFR-1, VEGFR-2 and VEGFR-3, the first two of which bind to VEGF-A. VEGF-induced

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endothelial cell proliferation and differentiation is mediated by the VEGFR-2 receptor.[4]

Many tumor cell lines secrete VEGF in vitro, and VEGF mRNA is expressed in carcinomas of the lung, breast, gastro-intestinal tract, bladder, kidney, ovary, endometrium and others. In this review, we focus on the role of VEGF in two urological malignancies: renal cell carcinoma (RCC) and prostate cancer (PCa).

Role of VEGF in kidney cancer

Cancer of the kidney is expected to account for an estimated 51190 new cases and 12890 deaths in 2007 in the United States[5] and 2% of new cancer cases worldwide. As much as 30% of the patients are likely to have metastatic disease at diagnosis.[6] The majority of these patients need systemic therapy,[7] but treatment options are limited. Therefore, effective drugs and accurate staging are crucial to ensure the best possible management of RCC.

The role of VEGF in the development of kidney cancer

The von Hippel Lindau (VHL) pathway plays a critical role in RCC. The VHL gene encodes a cytoplasmic protein that acts as an oxygen sensor. In conditions of normoxia and normal VHL function, VHL forms a multiprotein complex that binds to the transcription factor hypoxia inductible factor (HIF) 1-α, tagging it for degradation.[8] Under hypoxic conditions, the VHL protein complex is disrupted and HIF1-α is protected from degradation. The consequent accumulation of HIF1-α results in the overexpression of genes encoding VEGF, platelet-derived growth factor (PDGF) and transforming growth factor-α (TGF-α).[9] The complete inactivation of the VHL gene, due to mutation or methylation, causes HIF1-α accumulation during normoxic conditions, which in turn leads to the inappropriate overexpression of proangiogenic factors, and the promotion of tumor cell proliferation and angiogenesis, Figure 1. VHL gene inactivation, which mediates over-expression of VEGF in approximately 80% of clear cell RCC patients, makes VEGF and its receptor interesting targets for novel RCC treatment strategies.

The therapeutic impact of VEGF in kidney cancer

Multiple approaches to block VEGF signaling in kidney cancer have been tested. VEGFR-specific small molecule tyrosine kinase inhibitors (TKIs), multikinase inhibitors (MKI) and monoclonal antibodies (Mabs) against VEGF have been evaluated in patients with RCC in phase II-III trials, Table 1.

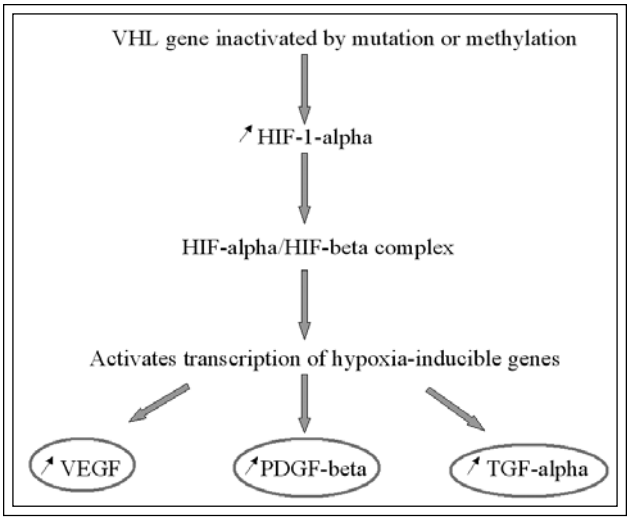

Figure 1. Illustration of the VHL/HIF/VEGF molecular pathway.

VEGFR-TKIs and MKIs

Sunitinib

Sunitinib (SU11248, SUTENT) is a small molecule TKI of VEGFR-2, PDGFR-β, FLT3 and c-Kit.[10] It is currently approved as a single-agent therapy in Canada, the United States and the European Union for patients with advanced RCC.

Sunitinib has been investigated in two single-arm multicenter phase II trials in patients with advanced RCC who had failed initial cytokine therapy.[11,12] The primary endpoint of both studies was the overall response rate, and the secondary endpoint was the duration of response. In the first study, 40% of patients had a partial response, with no complete responses. Median time to progression was 8.7 months. The most common treatment-related adverse events were neutropenia (13%), fatigue (11%), diarrhea (3%), nausea (3%) and stomatitis (2%).[11] In the second study, response rate was 34%, with only 1 complete response. There were 23/105 (22%) patients who demonstrated stable disease ≥ 3 months.[12] A phase III study was subsequently conducted, comparing sunitinib with IFN-α as a first-line treatment in 750 patients with advanced RCC.[13] The median progression-free survival was significantly longer in the sunitinib group (11 months) than in the IFN-α group (5 months) ($p < 0.001$). Moreover, patients in the sunitinib group reported a significantly better quality of life than did patients in the IFN-α group ($p < 0.001$).[13] Other studies with sunitinib are currently in progress, including combinations of sunitinib with immunotherapy and other targeted treatments.

TABLE 1. **Targeted therapies under investigation for the treatment of RCC**

Drug name	Target(s)	Mechanism	Clinical development stage
Sunitinib	VEGFR-2 PDGFR-β c-KIT Flt-3	TKI	Phase III trial in advanced RCC completed
Sorafenib	Raf-1 VEGFR-2 VEGFR-3 PDGFR RET Flt-3 c-KIT	MKI	Phase III trial in advanced RCC completed
Pazopanib	VEGFR PDGFR c-KIT	TKI	Phase III in advanced RCC
Bevacizumab	VEGF-A	Mab	Phase II alone in advanced RCC Phase III trial in combination with IFN-α in advanced RCC completed
Temsirolimus	mTOR	Rapamycin ester inhibitor of mTOR	Phase III trial in advanced RCC completed
Everolimus	mTOR	Serine/threonine kinase inhibitor of mTOR	Phase II in advanced RCC
AZD2171	VEGFR PDGFRβ c-KIT	TKI	Phase II in advanced RCC

Sorafenib

Sorafenib (NEVAXAR) is a MKI that simultaneously targets upstream receptor tyrosine kinases (VEGFR-2, VEGFR-3, PDGF-β, RET, fms-like tyrosine kinase-3, and c-KIT) and downstream serine/threonine kinases (C-Raf, B-Raf) in both the tumor cell and the tumor endothelium. Sorafenib is currently approved in Canada and the United States for the treatment of advanced RCC and in the European Union for the treatment of RCC in patients who have failed prior treatment with IFN-α or Il-2.[14]

Phase I studies showed that sorafenib was generally well-tolerated with mild to moderate toxicities. Pruritis and rash were the most common drug related adverse events, whereas diarrhea and fatigue were dose-limiting.[15,16] Recently, a phase II placebo-controlled randomized discontinuation trial in patients with metastatic RCC showed a significantly longer progression free survival (PFS) in patients who had received a continued treatment with sorafenib (24 weeks versus 6 weeks for placebo, $p = 0.0087$).[17] Based on these results, sorafenib was evaluated in a phase III, second-line trial, the Treatment Approaches in Renal Cancer Global Evaluation Trial (TARGET).[18] The primary objective was overall survival, the secondary objectives were PFS, response rate, safety and tolerability. Patients were eligible if they had metastatic clear cell RCC and had failed one prior systemic therapy. Sorafenib demonstrated a significant increase of median PFS compared with placebo (5.5 versus 2.8 months, $p < 0.001$). A response to treatment or a stability of the disease was achieved in 84% of patients receiving sorafenib versus 55% of patients receiving placebo. Finally, sorafenib showed a trend towards improved overall survival, with a 39% improvement over placebo. However, the potential of sorafenib versus IFN-α as a first-line treatment has not been demonstrated in a phase II clinical trial.[19] In this trial, the PFS was not statistically significant between the two groups. Nevertheless, a possible benefit from sorafenib dose escalation needs further investigation.

Others TKIs and MKIs are currently under investigation. Pazopanib is a TKI of VEGFR-1, VEGFR-2 and VEGFR-3 that is generally well tolerated, hypertension and hemorrhage being the most frequently observed adverse events. It is currently investigated in

a phase III trial comparing pazopanib versus placebo in patients with locally advanced and/or metastatic RCC.

Anti-VEGF Mabs

Bevacizumab

Bevacizumab (AVASTIN) is a recombinant humanized Mab that binds to all plasmatic VEGF-A isoforms, thus depriving VEGFRs of their ligand and inhibiting angiogenesis. Bevacizumab was the first anti-VEGF agent to be approved by the FDA/EMEA, in combination with 5-Fluorouracil in metastatic colorectal cancer. It is also approved for the treatment of unresectable, locally advanced, recurrent or metastatic non-squamous, non-small cell lung cancer. Bevacizumab was evaluated in a randomized, double-blind placebo-controlled phase II trial in patients with advanced RCC. The primary endpoints were response rate and time to progression (TTP). High-dose bevacizumab significantly prolonged TTP compared with placebo (4.8 versus 2.5 months, $p < 0.001$). TTP was also improved with low-dose regimens of bevacizumab, but the difference was not significant. There was no difference in overall survival between groups, possibly because patients in the placebo group whose disease progressed were allowed to take bevacizumab. The authors reported minimal toxic effects. Hypertension and asymptomatic proteinuria were the predominant adverse events.[20] The results of a double-blind phase III study of bevacizumab in combination with IFN-α versus IFN-α alone as first-line therapy in patients with metastatic RCC were recently presented to the public.[21] In this study, 649 nephrectomized patients were randomized in the two treatment arms. The addition of bevacizumab to IFN-α significantly increased PFS (10.2 versus 5.4 months, $p < 0.001$). However, 28% of the patients receiving IFN-α with bevacizumab had discontinued treatment due to adverse events, compared to 12% of patients receiving IFN-α alone. Pyrexia, fatigue, skin rash and asthenia were the predominant adverse events.[21]

Other molecular targets

Other molecules targeting the VEGF pathway are currently under development. These include anti-VEGF antibody fragments (Fab) (ranibizumab), anti-VEGFR Mabs or Fabs, soluble VEGF decoy receptors, aptamers which bind VEGF, and ribozymes or antisense oligonucleotides which specifically target VEGF mRNA.[22] A soluble form of VEGFR, sFLT-1 (soluble FMS-like tyrosine kinase-1), is a potent antagonist of VEGF. Therefore, it has been suggested that sFLT-1 gene transfer could induce an antiangiogenic effect and could have a therapeutic effect in cancer. Yoshimura et al[23] constructed an adenovirus vector which expressed sFlt-1 protein. They reported that the intramuscular administration of this vector inhibited lung metastasis in a murine model of RCC.

Components of other signaling cascades have also emerged as promising targets in RCC. One of these, the mammalian target of rapamycin (mTOR), is a serine-threonine kinase. mTOR activation has been shown to increase HIF-α gene expression, thus the overexpression of VEGF. Temsirolimus, an inhibitor of mTOR, has been evaluated in a phase III trial comparing temsirolimus, IFN-α, and temsirolimus plus IFN-α as first line therapy in patients with advanced RCC. Patients who received temsirolimus alone had longer overall survival ($p = 0.008$) and PFS ($p < 0.001$) than did patients who received IFN-α alone. Overall survival in the combination therapy group did not differ significantly from that in the IFN-α group ($p = 0.7$).[24]

Another potential target is the placenta growth factor (PlGF). Indeed, some authors suggested that PlGF enhanced pathologic angiogenesis by initiating crosstalk between VEGFR-1 and VEGFR-2. For example, using human cancer cell lines transfected with PlGF-2 full-length cDNA, Xu et al[25] showed that PlGF overexpression decreased VEGF homodimer formation and inhibited tumor progression. The PlGF pathway could therefore be used in future treatment strategies in patients with RCC.

Perspectives

In patients with locally aggressive RCC, the high recurrence rate after nephrectomy underlines the need for adjuvant therapy. Three large phase III trials are currently in development to evaluate the long-term safety and efficacy of kinase inhibitors as adjuvant therapy for RCC, the ASSURE trial (**a**djuvant **s**orafenib or **s**unitinib in **u**nfavorable **re**nal cell carcinoma), the STAR trial (**s**unitinib **t**rial in **a**djuvant **r**enal cancer), and the SORCE trial (**so**rafenib versus placebo in patients with **r**esected primary renal **ce**ll carcinoma).

Predictive and prognostic value of VEGF in kidney cancer

The development of adjuvant treatment strategies implies to identify patients at high risk to better determine those who will take a benefit from these new treatments. Whereas prognostic markers reflect the natural history of the disease independently of the

treatment received, predictive markers reflect the impact of a therapeutic intervention.

In recent years, a variety of prognostic markers have been identified. These include tumor grade, histological subtype, performance status and localized symptoms. Consequently, some authors have attempted to create models to stratify patients and predict outcome postnephrectomy.[26-30] Kattan et al[28] proposed a prognostic nomogram including T stage, tumor grade and the Eastern Cooperative Oncology Group (ECOG) performance status. This nomogram stratified patients into three subgroups of low, intermediate and high risk. Another nomogram, the Stage, Size, Grade and Necrosis (SSIGN) was developed at the Mayo Clinic and was subsequently chosen to be used in the clinical trial SORCE. More recently, the University of California, Los Angeles (UCLA) Integrated Staging System (UISS) was developed to include survival of patients with both localized and metastatic disease. This last nomogram was externally validated in an international, multicenter study,[29] and may also be useful for risk and outcome analysis. It will be used in the clinical trials ECOG2805 and STAR. However, no validated prognostic system includes yet angiogenesis markers. Ongoing work at UCLA is directed at identifying and incorporating relevant biomarkers into the UISS using microarray analysis.[30] The most promising molecular markers identified with the use of tissue microarray analyses include the members of the VEGF family of proteins and receptors. Indeed, it has been suggested that tumor subtypes of RCC were showing different VEGF expression profile. Using microarray analysis, Leppert et al[31] compared the expression of VEGF-A, VEGF-C, VEGF-D, VEGFR-1, VEGFR-2 and VEGFR-3 in samples of clear cell and papillary RCC. They found higher mean expression of VEGF-A and VEGFR-2 in papillary RCC tumors as compared with clear cell tumors. However, samples from clear cell tumors had higher mean expression of VEGF-D, VEGFR-1, VEGFR-2 and VEGFR-3 within tumor-associated endothelium than papillary tumors. The expression of the individual proteins from the VEGF family may also provide a risk profile for the development of metastases. It has been suggested that the expression of VEGFR-1 and -2 by tumor-associated endothelium was predictive of distant metastases whereas that of VEGFR-3 was more predictive of lymph node metastases.[32] VEGF and VEGFR profiles of expression may therefore be useful indicators of tumor subtype and disease stage.

If prognostic markers help to select patients before therapy, predictive markers need to be incorporated into staging systems to allow targeted therapies to be directed towards appropriate patients. Indeed, searching for markers of non-benefit for a selected therapy could spare non-responding patients from a useless toxicity. However, no true predictive factor has yet been identified in advanced RCC. VEGF level has been evaluated as a potential predictive biomarker of anti-angiogenic therapy. However, it is unclear how VEGF level fluctuates during treatment. In the TARGET trial, sorafenib showed a significant PFS benefit versus placebo. Based on these results, Bukowski et al[33] compared the PFS between patients with high (> 131 pg/ml) and low (< 131 pg/ml) blood VEGF level. They found that patients with high blood VEGF had a trend towards greater PFS benefit with sorafenib versus placebo. However, both high and low baseline VEGF groups benefited from sorafenib versus placebo.[33]

Whether markers of angiogenesis could help to prognosticate survival or predict response to anti-angiogenic therapy is still questionable and needs further investigation.

Role of VEGF in prostate cancer

The interest for VEGF in PCa came from the observation that androgens regulate VEGF expression not only in the normal prostate, but also in PCa.[34-38] It has also been shown that castration reduced endothelial cell numbers and endothelial cell proliferation in the prostate, which suggests a regulation of angiogenesis by androgens.[39] Moreover, studies measuring microvessel density in RP specimen from patients treated for PCa have suggested a correlation between angiogenesis and biological aggressiveness.[40,41] Collectively, these data suggest that VEGF as well as angiogenesis may play an important role in the early progression of PCa. Some authors have investigated the value of VEGF as a screening test for PCa, as a tool for PCa staging, and as a target for therapeutic strategies of PCa.

The diagnostic value of VEGF

It has been suggested that VEGF produced from normal prostatic tissues might substantially contribute to plasma levels, especially in patients with early stage PCa.[42] However, the diagnostic value of VEGF in patients with suspicion of prostate cancer is still debated. Duque et al[43] measured plasma VEGF in 26 healthy controls and in 80 patients with PCa (54 patients with clinically-localized cancer and 26 patients with metastatic cancer). In their study, median plasma VEGF was 28.5 pg/ml in patients with metastases, 7 pg/ml

in patients with localized disease, and 0 pg/ml in controls. Similarly, Shariat et al[44] measured plasma levels of VEGF in 40 healthy controls, 215 patients with clinically-localized prostate cancer, and 9 patients with untreated metastatic prostate cancer. These authors found that plasma levels increased incrementally from healthy controls to patients with localized cancer to those with metastases.

These studies suggest an association between plasma VEGF levels and PCa. However, in the studies of Duque et al and Shariat et al, the controls were considered as free of PCa because they had normal digital rectal examination and normal PSA. They did not undergo prostate biopsies. It was therefore difficult to assess the real diagnostic value of VEGF for PCa. Our team has recently analyzed serum levels of VEGF in 47 patients who underwent prostate biopsies for clinical and/or biological suspicion of PCa.[45] Prostate biopsies revealed the presence of PCa in 27 patients (including 22 localized tumors), and benign prostatic tissue in the remaining 20 patients. Serum VEGF levels in men with PCa were not statistically different from those in men without PCa on prostate biopsies (69.5 pg/ml versus 55 pg/ml, p = 0.55). This finding suggests that VEGF serum level cannot help to diagnose localized PCa. It is noteworthy that in our series VEGF was measured in serum instead of plasma. This could partly explain the discrepancy between our results and those previously reported.

In summary, the usefulness of VEGF as a marker of clinically-localized PCa is still under investigation. Although VEGF plasma level is increased in patients with clinically-localized PCa, its clinical value as a screening test has not been clarified.

The prognostic value of VEGF

As VEGF is involved in PCa growth, some authors suggested that this factor could be a useful prognostic marker for pretherapeutic staging. Indeed, several studies have showed that VEGF expression in PCa tissue, as well as VEGF plasma levels, correlate with disease aggressiveness. Duque et al[43] reported a trend for VEGF plasma level to be higher in patients with high Gleason grade patterns on RP specimens. Furthermore, in their study the patients with PSA levels greater than 20 ng/ml had significantly higher VEGF compared to those with lower PSA levels. These data are consistent with the findings of Shariat et al,[44] who found that plasma levels of VEGF were significantly elevated in patients with Gleason score ≥ 7 and/or extraprostatic extension. In addition, preoperative VEGF was associated with lymph node involvement and with biochemical progression after surgery. These results suggest that preoperative plasma VEGF may improve early identification of patients presenting with lymph node metastasis.

The expression of VEGF and/or its receptor VEGFR in prostatic tissue have also been showed to be associated with tumor Gleason grade, lymph node metastasis, and progression-free survival.[38,46] One of the mechanisms that leads to lymph nodes metastases is the formation of lymphatic vessels within the tumor. Two members of the VEGF family, VEGF-C and VEGF-D, are associated with lymphangiogenesis. Their effect involves VEGFR-3. Tsurusaki et al[46] showed a significant association between VEGF-C expression and lymph node metastases in human prostate carcinoma cells. They also observed that the number of vessels expressing VEGFR-3 increased when the tumor expressed VEGF-C. Similarly, Li et al[38] measured VEGFR-3 expression in malignant tissue from 640 RP specimens. PCa with high-level expression of VEGFR-3 was more frequently associated with a higher Gleason score, higher PSA level, and lymph nodes metastases. Furthermore, the 5-year recurrence free-survival was significantly higher in patients with low expression of VEGFR-3 than in those with high expression (77.3% versus 69.6%, p = 0.037). The tissular expression of VEGF has also been assessed on prostate biopsies. Recently, a group from UK evaluated the VEGF tissular expression on the prostate biopsies from 50 men with locally advanced PCa (T3 N0 M0, Gleason score >/=6), who received radiotherapy alone as primary treatment. They reported that high VEGF expression on prostate biopsies was associated with increased Gleason score and with disease-specific survival (p = 0.035). However, in their study, high VEGF expression was not associated with biochemical failure after radiotherapy. They concluded that high VEGF expression on prostate biopsies may enable to identify patients at high risk of recurrence after radiotherapy, and thus help to select patients who may benefit from additional treatment approaches.[47]

There is evidence that VEGF expression is associated with metastases. Indeed, patients with metastatic PCa have higher plasma VEGF levels than those with clinically localized disease.[43,44] In a recent study, Peyromaure et al[48] compared the expression of VEGF-A between a group of 17 patients with localized PCa who developed bone metastases after RP (group 1) and a second group of 23 patients with localized PCa and no evidence of metastases after RP (group 2). At the time of RP, no patient had clinical or radiological evidence of lymph node involvement or bone metastases, and none

had had hormone or radiation therapy. In group 1, the median interval between RP and the occurrence of bone metastases was 48 months. No patient from group 2 had any biological recurrence after RP with a median follow-up of 106 months. The two groups had similar tumor characteristics in terms of PSA level, Gleason score and pathologic stage. VEGF-A expression was significantly higher in group 1 than in group 2 ($p = 0.046$). Moreover, in logistic regression analysis, VEGF-A expression was the most significant predictive factor of cancer progression after RP.

The therapeutic impact of VEGF

Recent advances in the understanding of how castration acts through the VEGF system to inhibit angiogenesis may provide new treatment strategies in metastatic PCa. Although androgen ablation and secondary hormonal therapies are effective in treating metastatic PCa, the options for hormone-refractory disease are limited. To date, chemotherapy has been shown to improve quality of life in symptomatic patients, however the survival benefit is still controversial.[49] Petrylak et al[50] showed an improvement of nearly 2 months with the combination of docetaxel and estramustine compared to the combination of mitoxantrone and prednisone in men with metastatic androgen-independent PCa. Another study showed an improvement in survival and quality of life in patients with metastatic hormone-refractory PCa treated with docetaxel plus prednisone compared to mitoxantrone plus prednisone.[51] Docetaxel-based chemotherapy is now the standard of care.

Thalidomide (α-N{phthalimido} glutarimide [$C_{13}H_{10}N_2O_4$]) is a synthetic glutamic acid derivative that was initially used as an over-the-counter sedative-hypnotic. It was used for pregnancy-associated morning sickness but caused teratogenicity and neuropathies and was taken off the market. However, thalidomide was subsequently reintroduced to clinical practice in 1998 for the treatment of erythema nodosum leprosum, and has been evaluated in the treatment of advanced PCa. Although its mechanism is poorly understood, thalidomide is believed to have antiangiogenic properties. These are likely due to inhibition of basic fibroblast growth factor and VEGF. In a phase II study comparing docetaxel plus thalidomide with docetaxel alone, a response rate of 53% was reported in the combination arm compared to 37% in the docetaxel-only arm. The median PFS was 5.9 months for the combination and 3.7 months for docetaxel alone.[52]

SU5416 (semaxinib) is a MKI targeting VEGFR-3, c-KIT and FLT3R. Phase I studies showed that the drug was generally well tolerated but required concomitant administration of dexamethasone to prevent hypersensibility reactions.[53] However, a randomized phase II study comparing dexamethasone alone with SU5416 and dexamethasone did not detect any modifying effects of SU5416 and the authors decided to halt further evaluation of SU5416 in PCa.[54]

Additional studies of antiangiogenic agents in hormone-refractory PCa include the humanized Mab to VEGF, bevacizumab. The Cancer and Leukemia Group B study 90006 treated patients with bevacizumab in combination with docetaxel, and found the regimen to be active with a 53% partial response rate in measurable disease and a 65% biochemical response rate.[55] Other strategies consist in the suppression of VEGF synthesis. Takei et al[56] developed a novel VEGF blockade system using RNA interference. These authors planned to suppress the synthesis of VEGF in the human PCa cell line PC-3 using interfering RNA, and to evaluate its therapeutic significance in a xenograft model (athymic nude mice). They showed that the interfering RNA to VEGF successfully inhibited the secretion and expression of VEGF in PC-3, leading to the potent suppression of tumor growth in its xenograft model. They concluded that VEGF blockade by interfering RNA could represent a new therapeutic option.

In conclusion, the recent advances in the understanding of how VEGF system is involved in metastatic PCa may provide new effective treatment strategies for patients with hormone-refractory disease. However, the clinical benefit of these new molecules has yet to be demonstrated.

Conclusions

The VEGF system has a major role in angiogenesis regulation. VEGF is directly involved in the development of RCC through the dysregulation of the VHL gene. There is also strong evidence that VEGF is involved in PCa growth process.

In patients with metastatic and locally advanced RCC, molecules targeting the VEGF pathway have shown strong results in phase II and III clinical trials. In the next future, these molecules could also be used in adjuvant treatment strategies after surgery. Moreover, the use of VEGF as a staging tool could enable to better select patients for appropriate treatment.

In patients with PCa, the clinical value of VEGF in the early diagnosis of localized disease has not been demonstrated. Its usefulness as a prognostic factor is highly suggested, but remains to be clarified. Additionally, new treatment strategies targeting the VEGF pathway are currently under investigation. □

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