The Value of Anti-angiogenics in Bladder Cancer Therapy

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Abstract
The therapy of metastatic bladder cancer (BC) mainly relies on platinum-based chemotherapy with very limited options like vinflunine in the second line. Therefore, there has not been much change in the median survival of this patient cohort within the last decades. Angiogenesis is a well-proven patho-mechanism in BC. Different angiogenic pathways have been elucidated within the last 20 years, among them vascular endothelial growth factor (VEGF), angiopoietin/Tie, matrix metalloproteinases (MMPs), fibroblast growth factor (FGF), thrombospondin 1 (TSP1), and hypoxia-inducible factor (HIF) as the most prominent ones. In order to be able to understand the mechanisms of novel compounds, it is helpful to have a basic knowledge of the relevance of these signaling pathways in the field of BC. Therefore, we not only sum up the majority of clinical studies on anti-angiogenics in BC but also explain the most important pathways responsible for bladder tumor angiogenesis in this chapter.

Many established anti-angiogenics like bevacizumab, sunitinib, sorafenib, afiblercept, pazopanib, and vandetanib have been tested in clinical trials for BC. Furthermore, the pipelines are filled with clinical trials on novel anti-angiogenic drugs like ramucirumab, icrucumab, regorafenib, nintedanib, and many more. However, no compound has yet proven significant single-agent efficacy. Therefore, up to now, no anti-angiogenic drug has been approved for BC therapy.

Consequently, future clinical trials will not only have to test for new anti-angiogenics, but also for different treatment algorithms as well as combination therapies. Although most of the studies showed disappointing overall results, subcohorts had a significant benefit. Therefore, novel approaches should increasingly focus on identifying patient subgroups with the greatest susceptibility to the respective anti-angiogenic therapy.

Keywords
Bladder cancer • Urothelial carcinoma • Sorafenib • Sunitinib • Ramucirumab • Pazopanib • Afiblercept • Bevacizumab • VEGF • FGF • Angiopoietin

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Introduction

Bladder cancer (BC) is the 11th most common cancer entity and accounts for approximately 150,000 deaths each year worldwide. The incidence is about four times higher in the male population, which makes BC the fourth most common malignancy in men. In Europe and North America, about 90% of BC are urothelial carcinoma (UC), followed by squamous cell carcinoma (SCC). By far the most relevant clinical risk factor is smoking followed by occupational exposure to different toxins. About 75% of patients with BC are initially diagnosed with non-muscle-invasive BC (NMIBC) (pTa, CIS, pT1). The most common symptom finally leading to the diagnosis of BC is macrohematuria.

NMIBC is treated endoureologically with transurethral resections of the bladder (TUR-B) as well as intravesical chemotherapy. Patients with high-grade NMIBC are eligible for intravesical immunotherapy with BCG (bacillus Calmette-Guérin) for up to 3 years. Follow-up of NMIBC in order to prevent both progression to MIBC and recurrence is based on regular urethrocystoscopy and urine cytology. This makes BC one of the most expensive cancer entities. Although much effort has been invested into novel diagnostic and prognostic markers, none has been implemented into clinical practice yet.

Gold standard for muscle-invasive bladder cancer (MIBC) is still radical cystectomy (RC). Available data on neoadjuvant chemotherapy is partially contradictory with absolute 5-year OS improvement between 5% and 8% (Babjuk et al. 2016). Adjuvant therapy algorithms are based on cisplatin in the first line, in combination with gemcitabine (GC), paclitaxel (PCG) or methotrexate, vinblastine, and Adriamycin (MVAC). As second-line treatment, only vinflunine is established at the moment. Whereas 5-year survival in NMIBC ranges around 90%, this decreases to <50% in MIBC. In metastatic disease median survival is around 15 months only. Interestingly, the huge difference in the aggressiveness between low-grade NMIBC and high-grade MIBC is paralleled on the molecular level by two distinct pathways. While in papillary low-grade tumors activating FGF3 mutations are frequently found, TP53 mutations are more common in carcinoma in situ (CIS) and MIBC (Knowles and Hurst 2015).

Compared to other cancer entities, there has been only very limited therapeutic progress in the field of BC. In 2016, the PD-1/PD-L1 inhibitor atezolizumab has been approved by the FDA for locally advanced or metastatic BC. As the last major clinical breakthrough, BCG intravesical immunotherapy has been implemented nearly 40 years ago; every opportunity that might ultimately lead to the improvement of BC therapy has to be embraced.

The role of tumor angiogenesis as a major driver for BC pathogenesis is broadly accepted. In the first part of this chapter, we want to elucidate the role of different angiogenic pathways in BC. Besides the VEGF pathway, fibroblast growth factor, angiopoietins, matrix metalloproteinases, as well as hypoxia-inducible factors are central stakeholders. In the following main part, both completed clinical trials and open studies on anti-angiogenic therapies will be presented in detail.
Angiogenesis in Bladder Cancer:
Microvessel Density and Other Early Approaches

Angiogenesis is a central mechanism in the pathogenesis of BC and therefore also a highly attractive therapeutic target (Bochner et al. 1995). For more than 20 years, studies are being published on angiogenesis in BC. At the beginning, similar to other cancer entities, anatomical angiogenesis markers like microvessel density (MVD) were correlated with different clinical parameters. In the following years, as angiogenesis became one of the main focuses in cancer research, VEGF and other prominent pathways were investigated in the context of BC.

The most direct way to evaluate angiogenesis is the histopathologic assessment of endothelial cells. Within the last years, different approaches like the MVD, microvessel count (MVC), and the vessel surface area (VSA) have been used for this purpose.

An increase in MVD was correlated with advanced BC stage and grade and worse prognosis (Canoglu et al. 2004; Chaudhary et al. 1999; Sankhwar et al. 2015). Compared to NMIBC, MVD is elevated in MIBC (Shirotake et al. 2011). A study of 61 patients with NMIBC and MIBC significantly associated with high MVD with reduced survival. Furthermore, high MVD in NMIBC was correlated with progression to MIBC (Goddard et al. 2003). In MIBC, MVD was shown to be a prognostic marker for disease recurrence after radical cystectomy (RC) (Inoue et al. 2000a). On the other side, elevated VSA could be correlated with longer disease-free survival rates in the same cohort (Bertz et al. 2014). There are also studies showing an increased MVD in organ-confined tumors compared to T3–4 BC as well as nodal negative compared to lymph node-positive BC (Herrmann et al. 2007). Intravesical immunotherapy with BCG in high-grade NMIBC is able to prevent progression and recurrence. However, as this instillation therapy comes with the risk of significant side effects, prognostic markers for identifying possible therapy responders are needed. MVD has been shown to be an independent prognostic marker for recurrence after BCG-therapy (Ajili et al. 2012).

These results clearly illustrate the challenge of several coexisting scores for assessing clinical relevant angiogenesis. On the one hand, the partially contradicting data on tumor angiogenesis might be based on different quantitative markers for angiogenesis. On the other hand, several studies did not evaluate the MVD blinded, which might lead to bias. Therefore, simply correlating clinical data with just “more” or “less” angiogenesis might not be sufficient in future. Most probably the focus might shift on describing different aspects of angiogenesis and tumor microvessels like architecture, vessel count, and diameter as well as interplay with perivascular components like smooth muscle cells, extracellular matrix, and pericytes. To sum up, one can say that MVD as the most reliable marker for angiogenesis is associated with advanced disease and dismal prognosis.

Compared to angiogenesis, lymphangiogenesis is much less investigated in BC. However, lymphovascular invasion is a scientifically proven prognostic factor in BC and might contribute to metastatic spread. Indeed, VEGF-C, well known for its role in controlling lymphangiogenesis, has been shown to be an independent prognosticator for adverse oncologic outcome. Furthermore, high VEGF-C expression in histopathological BC specimen could be correlated with stage, MVD, and lymph node metastasis (Suzuki et al. 2005). As most patients with BC die of metastatic disease, the inhibition of lymphangiogenesis might be a novel therapeutic target (Benoit et al. 2015; Yang et al. 2011).

Angiogenic Pathways in Bladder Cancer

VEGF/VEGFR was the historically first pathway associated with angiogenesis and also the first used as a target for anti-angiogenics. In NMIBC, elevated serum levels of VEGF were significantly associated with a decrease in cancer-specific survival (CSS). Moreover, serum VEGF levels at the top quintiles were shown to be an independent
prognostic marker for overall survival (OS) and CSS (Puntoni et al. 2016).

In BC patients, urine levels of VEGF are not only significantly elevated compared to control groups, but are also positively correlated with stage. Tissue VEGF levels were correlated with urine VEGF levels in this study (Sankhwar et al. 2015).

In NMIBC, both tissue and serum protein levels of VEGF are upregulated compared to controls (Kozakowska et al. 2016; Sankhwar et al. 2015). RNA and protein expression of VEGF and its receptor VEGFR1 are elevated in BC tissue compared to control groups. With advanced stage and grade as well as in MIBC compared to NMIBC, VEGF expression in human histopathological specimen is significantly higher. However, recurrence-free survival as a clinical endpoint could not be significantly associated with the expression of these angiogenic molecules in this study (Yang et al. 2004). The role of the VEGF pathway in BC becomes even more complicated, as VEGF is upregulated in NMIBC compared to MIBC, whereas for VEGFR the opposite can be seen, as VEGFR is upregulated in MIBC compared to NMIBC (Kopparapu et al. 2013). In a cohort of 72 patients with UC, VEGFR2 expression in histopathological specimen could be correlated with stage and invasiveness, confirming the conclusions from abovementioned studies (Xia et al. 2006).

In summary, VEGF signaling is increased in BC and was correlated with clinical outcome in urine, serum, and histopathological specimen.

Endocan (ESM1), a protein preferentially expressed in endothelial cells, is overexpressed in different cancer types like lung, renal cell, and hepatocellular cancer. By binding to its receptor VEGFR2, VEGF regulates the expression of endocan in endothelial cells. Compared to benign bladder tissue, endocan levels are increased in BC microvessels and could be correlated with both staging and recurrence-free survival in BC. Therefore, external validation is required to evaluate endocan as a prognostic biomarker (Roudnicky et al. 2013; Yang et al. 2015). Moreover, serum and urine endocan levels are increased in BC compared to control groups. However, diagnostic sensitivity for BC only ranges between 50% and 62%. The specificity of this potential diagnostic marker is reduced, as endocan expression in serum and urine is increased in patient with urinary tract infections (Laloglu et al. 2016).

One of the first proven drivers for angiogenesis in both physiological and pathological conditions is hypoxia. Among the most prominent components of this signaling pathway are the hypoxia-inducible factors (HIF). These transcription factors stand upstream of the VEGF pathway, by which HIF is able to activate neo-angiogenesis. In NMIBC, both HIF-1α and HIF-1β are elevated on RNA level in BC tissue compared to control groups. Another study investigated HIF-1α in urine samples, demonstrating a significant gain in BC sensitivity when HIF-1α is combined with urine cytology. However, there was no correlation between HIF-1α and MVD in this study (Badr et al. 2013). HIF-1α might also be of use as a diagnostic marker, as the expression in human BC tissue has been correlated not only with VEGF and MVD, underlining the significance of this pathway for angiogenesis in BC, but also with stage and grade (Deniz et al. 2010). The significant association between HIF-1α and MVD and VEGF was shown in a study including 99 patients with UC. Additionally, both HIF-1α and MVD proved to be independent factors for disease-free survival (DFS) (Chai et al. 2008). Immunohistochemical expression of HIF-1α was higher in both MIBC and CIS (Ioachim et al. 2006). For upper tract urothelial carcinoma (UTUC), HIF-1α expression was also found to be a prognostic factor for oncologic outcome (Ke et al. 2008). Although HIF might not be used as a target for anti-angiogenic therapy in the near future, this transcription factor might help us to identify patients susceptible to novel anti-angiogenics.

Heme oxygenase is an enzyme important for the conversion of heme to biliverdin. However, several studies indicated an additional role of heme oxygenase 1 (HO-1) in tumor angiogenesis, shown for glioma, prostate cancer, and pancreatic cancer. Interestingly, heme HO-1 has also been shown to be elevated in NMIBC (Kozakowska et al. 2016). Increased HO-1 protein levels are
correlated with an increase in MVD in human BC specimen. As inhibition of HO-1 with zinc protoporphyrin (ZnPP) inhibits angiogenesis in vivo in BC, ZnPP might be of clinical relevance (Miyake et al. 2011). This is supported by other studies on this component, which could show that ZnPP not only decreases angiogenesis but far more important also tumor growth (Cheng et al. 2016).

Another mediator of angiogenesis in BC seems to be the macrophage migration inhibitory factor (MIF). MIF is a pro-inflammatory cytokine promoting both hypoxia-induced and non-hypoxic neo-angiogenesis. MIF mediates HIF-induced VEGF expression and activates tumor-associated macrophages (TAM) that are known to play a central role in angiogenesis (Chesney and Mitchell 2015). In a murine BC model, inhibition of MIF not only reduced the stage of BC but also angiogenesis, accentuating the relevance of this link in BC. The relevance of MIF for neo-angiogenesis was confirmed in different cancer entities like melanoma and breast, ovarian, gastric, hepatocellular, and lung cancer (Choudhary et al. 2013). As a phase I study evaluating an anti-MIF antibody is under way (NCT01765790), further studies will have to investigate the role of MIF in human BC.

The angiopoietin-tie (Ang-Tie) signaling system plays a central role for the equilibrium between neo-angiogenesis and vascular quiescence. The ligand angiopoietin 1 (Ang1) acts as an agonist for the mainly vascular-based receptor tyrosine kinase (RTK) Tie2 and mediates stabilization of the vasculature. In this simplified overview of this pathway, the antagonist Ang2 promotes neo-angiogenesis. However, the role of the Ang-Tie signaling system in BC angiogenesis is unclear so far. In a study comparing serum levels of different angiogenic molecules, Ang1 was significantly higher in patients with BC compared to control groups. The same study also found the soluble receptor Tie2 to be correlated with oncologic outcome (Szarvas et al. 2009). In NMIBC human tissue, Ang1 expression was shown to be significantly lower compared to the normal urothelium on both RNA and protein level, whereas VEGF expression was increased. Interestingly, high Ang2 expression was correlated with tumor recurrence in a multivariate analysis in this study, which could be verified by another study (Oka et al. 2005; Szarvas et al. 2008). These data fit to our current understanding of this pathway, where Ang1 inhibits angiogenesis and Ang2 acts as its antagonist. In a study comparing MIBC with NMIBC, both VEGF and Ang2, markers for increased angiogenesis, were elevated in NMIBC, whereas Ang1, the Tie2 ligand responsible for vessel stabilization and maturation, was elevated in MIBC. According to these results, there might be an angiogenic switch when BC becomes muscle invasive. Therefore, NMIBC might be characterized by a highly active vessel remodeling and angiogenesis, whereas in muscle-invasive stages, mature vessels are able to supply the tumor with a sufficient blood supply (Quentin et al. 2004). A quite new therapeutic approach which can be derived from abovementioned studies might be targeting vessel maturation instead of just inhibiting neo-angiogenesis. In conclusion, it is quite difficult to evaluate the data on the Ang-Tie system in BC, as this signaling pathway can promote angiogenesis via Ang2 signaling as well as mediate vessel quiescence via Ang1, and yet it is completely unclear which is more detrimental. Clinical studies on angiopoietin inhibitors like the peptibody trebananib (AMG 386) are performed for different solid tumors. However, according to our knowledge, there is no clinical study with the focus on BC for angiopoietin modulators at the moment.

Basic fibroblast growth factor (bFGF) is a well-known mediator of angiogenesis (Przybylski 2009). When UC cell clones with high bFGF expression were transplanted into mice, these clones were of significantly higher malignancy compared to controls (Chikazawa et al. 2008). In a clinical study, bFGF and VEGF in surgical specimen were found to be independent prognosticators for adverse oncologic outcome after neoadjuvant chemotherapy (Inoue et al. 2000a). Furthermore, a significant association between urinary bFGF and BC stage has been proven (Gravas et al. 2004; Zaravinos et al. 2012). Dovitinib, a tyrosine kinase inhibitor of FGFR3 and VEGFR2, is tested in a phase II study in a
cohort of BCG-refractory patients (NCT01732107). Another phase II study investigates JNJ-42756493, a pan-FGFR inhibitor in a cohort of metastatic UC (NCT02365597).

During the process of neo-angiogenesis, the perivascular space including basement membrane and extracellular matrix has to be remodeled. This complex and yet poorly investigated process is a predisposition for migrating endothelial cells, which are guided by angiogenic factors retained and subsequently released by the ECM. Important stakeholders controlling this remodeling machinery are matrix metalloproteinases (MMPs) and the respective inhibitors, tissue inhibitors of matrix metalloproteinases (TIMP). In peripheral blood leukocytes, elevated MMP9 was significantly associated with increased BC grade (Wieczorek et al. 2015). Interestingly, MMP9 expression in 131 patients with UC could be correlated with both stage and grade, with higher expression levels seen in advanced stage and high-grade tumors. This underlines the biological significance of MMP9 in BC angiogenesis (Donmez et al. 2009). In another study comparing MMP9 serum levels of BC patients with a healthy control group, MMP9 levels were not only significantly higher in the BC cohort, but also correlated with stage and grade (Guan et al. 2003). Additionally to MMP9, MMP1 seems to play a similar role in BC, as increased urine concentrations of MMP1 are seen in BC patients and high MMP1 levels were positively correlated with BC stage and grade (Durkan et al. 2001).

Among others, MMP9 expression is induced by heparin-binding epidermal growth factor-like growth factor (HB-EGF). Cancer cells expressing HB-EGF induce tumors with a higher vascularization (Ongusaha et al. 2004). As there are studies suggesting HB-EGF to act as a downstream target of VEGF, it might be worth evaluating HB-EGF as a novel target for anti-angiogenic therapy (Arkonac et al. 1998).

Interleukin-8 (IL-8) mediates tumor angiogenesis through tumor-infiltrating macrophages (Qazi et al. 2011). In BC, IL-8 inhibition reduces the expression of MMP9, which plays a relevant role in matrix remodeling. In a mouse model, inhibition of IL-8 by an antibody was able to reduce both tumor growth and MVD (Inoue et al. 2000b; Mian et al. 2003). The relevance of IL-8 in BC pathogenesis is underlined by a study showing IL-8 to be significantly elevated in the urine of BC patients compared to control groups as well as in MIBC compared to NMIBC (Sheryka et al. 2003). Summarizing, in the short and medium term, clinical relevance of MMPs and IL-8 might be mainly derived from their use as biomarkers and less likely from their therapeutic approaches.

In a murine BC model, the transcription factor Krüppel-like factor 5 (KLF5) has been shown to regulate VEGF. In the same study, the expression of KLF5 and VEGF correlated in human BC tissue, which makes KLF5 a possible novel target for anti-angiogenic therapy (Gao et al. 2015).

BLCA1 is a nuclear matrix protein used for BC detection. In human BC tissue, elevated BLCA1 expression has been correlated not only with clinical parameter like advanced stage but also angiogenic markers including VEGF, MMP9, and MVD (Feng et al. 2015). However, further studies are needed in order to decipher the relevance of KLF5 and BLCA1 for BC angiogenesis.

Angiotensin receptors are not only expressed in several tumors but might also play a significant role in angiogenesis (Miyajima et al. 2009). In BC, angiotensin II type 1 receptor (AT1R) expression in MIBC and high-grade NMIBC was higher compared to NMIBC and low-grade NMIBC. What is more, AT1R was significantly correlated to MVD, which makes AT1R a possible new target for anti-angiogenic therapy in BC (Shirotake et al. 2011).

Thrombospondin is a well-known inhibitor of angiogenesis (Lawler and Lawler 2012). In patients undergoing RC for BC, thrombospondin is not only downregulated but furthermore could also be correlated to oncologic outcome in a multivariate analysis (Shariat et al. 2010). Both advanced stage and grade are associated with decreased expression of thrombospondin. Interestingly, in the same study, VEGF and MMP9 were found to be alternated in inverse correlation to thrombospondin, underlining the significance of this pathway (Donmez et al. 2009). In NMIBC, thrombospondin was shown to be an independent
predictor for progression to invasive disease (Goddard et al. 2002). Androgens act as thrombospondin inhibitors, which makes them indirect mediators of angiogenesis. In murine in vivo models for BC, castration inhibited tumor growth significantly. However, the relevance for antiandrogen therapy for BC is completely unclear (Johnson et al. 2008). Thrombospondin has been used as an antiangiogenic agent in different phase I clinical studies against advanced tumors of different cancer entities, both as a single agent and within a combination therapy with bevacizumab and cisplatin/gemcitabine (Gietema et al. 2006; Gordon et al. 2008; Uronis et al. 2013). However, to our knowledge there are no open clinical trials for BC with thrombospondin-mimetic agents at the moment.

Endostatin, like thrombospondin, belongs to the group of endogenous angiogenesis inhibitors. Although the role of endostatin in BC has been investigated, the clinical relevance as a biomarker or even therapeutic target is largely unclear (Du and Hou 2003; Szarvas et al. 2012).

The role of microRNAs in BC, like in most of the other cancer entities, remains quite unclear although several groups have been working on this topic (Guancial et al. 2014). Murine in vivo experiments established microRNA-34a as both metastasis suppressive and anti-angiogenic. Moreover, microRNA-34a levels were also decreased in bladder cancer tissue (Yu et al. 2014).

**Targeting Angiogenesis in Bladder Cancer Clinical Trials**

Different clinical trials targeting BC angiogenesis have been performed. Therefore, anti-angiogenics have been used both as single agents and in combination with standard chemotherapy. However, only very few phase III trials were completed or are ongoing (Mazzola and Chin 2015; Pinto et al. 2010; Sonpavde and Bellmunt 2016). The following section gives an overview on the majority of clinical studies performed on anti-angiogenics for BC.

**Bevacizumab**

Bevacizumab most likely is the most prominent anti-angiogenic, interfering with the VEGF pathway. In a phase II study testing bevacizumab in addition to gemcitabine/cisplatin (GC) in a first-line chemotherapy setting for metastatic or unresectable UC, overall response rate was 72%, median progression-free survival (PFS) 8.2 months, and median overall survival (OS) 19.1 months (Hahn et al. 2011). An ongoing phase III trial compares GC chemotherapy for metastatic or unresectable BC with GC plus bevacizumab (NCT00942331).

**Aflibercept**

Another approach to target the VEGF system is aflibercept, a fusion protein able to neutralize different VEGF isoforms. In a phase II study, aflibercept was administered to a cohort of BC patients previously treated with a platinum-based chemotherapy. Unfortunately, there has not been a significant improvement of oncologic outcome (Twardowski et al. 2010).

**Sunitinib**

Sunitinib is a receptor tyrosine kinase (RTK) inhibitor targeted against different receptors, among them both VEGFR and PDGFR. In a multicentric, double-blinded phase II study, sunitinib versus placebo were investigated as a maintenance therapy with 6-month progression rate as the primary endpoint. Fifty-four patients were included after four to six cycles of chemotherapy with locally recurrent or metastatic BC. Although serum VEGFR2 levels were reduced under sunitinib maintenance, the 6-month progression rate was not reduced by the anti-angiogenic agent (Grivas et al. 2014). In addition, a phase II study tested two different schedules of sunitinib in a cohort of metastatic BC with previous chemotherapy. Although oncologic response was seen in some patients with tumor regression lasting between 0.6 and
23.4 months, overall results were disappointing, and the threshold of at least 20% of activity defined by RECIST was not achieved (Gallagher et al. 2010). Another phase II clinical trial tested the combination of gemcitabine, cisplatin, and sunitinib for BC in both the adjuvant and neo-adjuvant setting. However, the trial was closed due to excess toxicity of the combination therapy (Galsky et al. 2013).

**Everolimus**

A phase II study including 37 patients tested everolimus in a patient cohort of UC after failure of a platinum-based chemotherapy with disease control rate (CCR) as primary endpoint. Everolimus was well tolerated and DCR was 27% after 8 weeks. Importantly, efficacy was enhanced in a patient subcohort with higher initial angiopoietin-1 levels, which might be of utmost importance when selecting suitable patients for anti-angiogenic therapy in BC (Seront et al. 2012).

**Sorafenib**

A multicenter phase II study evaluated sorafenib in addition to conventional chemotherapy with GC compared to GC alone as first-line adjuvant chemotherapy. Primary endpoint was PFS in this study, including 89 patients. In the final analysis, no significant difference between the two arms in respect to ORR, median PFS, and OS was observed (Krege 2014). Sorafenib was also tested as first-line chemotherapy in metastatic UC in a phase II study. However, sorafenib did not show any significant improvements (Sridhar et al. 2011).

**Pazopanib**

Pazopanib is a multi-targeting RTK inhibitor with anti-angiogenic activity by targeting FGFR, PDGFR, and VEGFR. In a phase II study, pazopanib was tested in 19 patients with metastatic UC after previous chemotherapy. However, results were disappointing and the study was closed after the interim analysis (Pili et al. 2013). Another randomized phase II study compared pazopanib with paclitaxel in 131 patients with advanced BC and previous platinum-based chemotherapy. Primary endpoint was OS. The study was closed as futility criteria were fulfilled. In this trial, pazopanib did not prove to be superior to paclitaxel as second-line therapy (Powles 2016). Pazopanib was also tested in a single-arm phase II study (NCT01031875) in a cohort of platinum-based chemotherapy pretreated patients with metastatic UC. An objective response rate of 17.1% was reported in this study (Necchi et al. 2012). Interestingly, IL-8 levels were identified as a prognostic marker for oncologic response to pazopanib (Necchi et al. 2014).

**Cabozantinib**

Cabozantinib is a small molecular inhibitor targeting the VEGF and MET pathways. A phase II study for advanced/metastatic BC is under way, and study completion is estimated for August 2018 (NCT01688999). Interestingly, levels of regulatory T cells (Treg) in the peripheral blood before the administration of cabozantinib correlate with partial response (Apolo 2014).

**Ramucirumab/Icrucumab**

In a randomized, controlled phase II study (NCT01282463), enrolling 140 patients after platinum-based chemotherapy for advanced UC docetaxel was compared to the combination of docetaxel/ramucirumab and docetaxel/icrucumab (Petrylak 2016). PFS was used as the primary endpoint. Ramucirumab is a monoclonal antibody directed against VEGFR-2, inhibiting binding of all VEGF ligands. Icrucumab inhibits ligand interaction and subsequent phosphorylation of VEGFR-1. In this promising trial, combination of docetaxel with ramucirumab prolonged PFS compared to chemotherapy with docetaxel alone (5.4 months vs. 2.8 months). On account of these
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Conclusion

Treatment options and also prognosis for patients with advanced BC are still very limited up to now. As BC is the ninth most common malignancy, improvements are eagerly awaited. However, especially when compared to many other cancer entities, there has not been much innovation during the last decades.

Like in many other oncologic entities, anti-angiogenic therapies did not bring the expected and urgently needed improvements compared to standard care. Neither bevacizumab, sorafenib, sunitinib nor pazopanib significantly improved oncologic outcome in advanced or metastatic BC. To be clear, at the moment there is no anti-angiogenic therapy approved for BC. Still, there is good reason to be optimistic for anti-angiogenics in the midterm, with good results in a phase II study for ramucirumab and an ongoing phase III trial testing bevacizumab in addition to gemcitabine/cisplatin in the adjuvant setting. This optimism is supported by the evidence generated by a whole bunch of publications showing that angiogenesis plays a significant part in BC pathogenesis. Besides VEGF, Ang-Tie, FGF, TSP1, MMP, and HIF, there are still many more angiogenic signaling pathways unexplored in BC. Furthermore, several completely new compounds are tested in clinical studies, and results are eagerly awaited.

So where will we head in the future? First, as it becomes more and more evident that there will be no single anti-angiogenic for all patients with advanced BC, we will have to focus on biomarkers to identify subcohorts which are susceptible to the respective compound. Secondly, more consideration has to be given to combination therapies as well as different treatment sequences. Lastly, profound basic as well as translational research will have to be conducted to both identify new targets and understand mechanism of resistance to angiogenic treatments.

Cross-References

- Anti-angiogenesis and Cytotoxics
- Anti-angiogenic Cancer Therapy: Development of Resistance
- Anti-angiogenic Targets: Angiopoietin and Angiopoietin-Receptors
- Anti-angiogenic Targets: VEGF and VEGF-Receptors
- Anti-angiogenics and Radiation Therapy
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