Molecular Therapy in Urologic Oncology

Introduction

Molecular or ‘targeted’ therapy is considered to be a new strategy in medical oncology, supplementing the traditional options surgery, irradiation, and chemotherapy. To qualify as targeted therapy, three requirements should be met: the target should be an important metabolic pathway, it should be measurable, and interaction with the target should result in clinical benefit [1]. Targeted therapy differs from traditional antineoplastic chemotherapy in several ways. It has a different toxicity profile (less severe side effects, different spectrum, frequently rash or hand-foot syndrome). Most small-molecule agents can be given orally and interact with one or more molecular targets, usually involved in cellular signalling pathways. Treatment with these agents results in a different response pattern (stabilization of disease rather than measurable remission). Often, there is no clearly defined dose-response relationship. The proof of specific target expression, for instance by immunohistochemistry, enables an individualized treatment, sparing the treatment side effects in patients not expressing the target molecule [2–7].

Several approaches can be used for the interaction with target molecules in genito-urinary cancer treatment. These may consist of competitive inhibition (example: atrasentan, an endothelin receptor antagonist), antibody
binding to a ligand (example: bevacizumab, an antibody against vascular endothelial growth factor; VEGF), antibody binding to a receptor (example: trastuzumab, an antibody against Her2; ErbB2), inhibition of the receptor tyrosine kinase (example: gefitinib, an inhibitor of the receptor of epidermal growth factor; EGF), inhibition of tyrosine kinases in the downstream signalling pathway (example: temsirolimus, an inhibitor of mammalian target of rapamycin; mTOR), or application of a ligand to a receptor (example: calcitriol, binding to the calcitriol receptor). During recent years, several targeted treatment strategies have been evaluated in urologic oncology, with differing success. Some of them offer a treatment option in hitherto almost untreatable disease states and might become a new standard of care in the years ahead. In this article, we summarize the currently available targeted treatment options in urologic oncology. In the rapidly growing field of molecular therapy, we focused on therapies with proven or probable value in clinical practice.

Renal Cell Carcinoma

In the field of urologic oncology, the greatest body of evidence is available supporting targeted therapy of advanced renal cell carcinoma. This disease is notoriously resistant to conventional chemotherapy and radiotherapy and is, therefore, particularly difficult to treat, when surgery was unable to control the disease. The majority of clear cell renal cell carcinomas, the by far most common type of kidney cancer, harbour a loss of function of the von Hippel-Lindau gene product (chromosome 3p deletion, suppressed expression or inactivating mutations of the gene). In normal tissue, the von Hippel-Lindau protein is involved in the regulation of responses to hypoxia [2, 4]. Figure 1 illustrates the signalling pathway activated by the loss of function of this gene [2, 8]. Several targeted therapies have shown clinical activity in renal cell carcinomas. Molecular treatment may target the ligand of the VEGF receptor (bevacizumab is a monoclonal antibody against VEGF receptor), receptor tyrosine kinases VEGF receptor and platelet-derived growth factor (PDGF) receptor (sunitinib and sorafenib target these receptors), or it may intervene in the downstream signalling pathway (temsirolimus is an inhibitor of the mTOR, a serine-threonine protein kinase involved in the downstream signalling pathway). Besides its inhibitory effect on receptor tyrosine kinases, the multikinase inhibitor sorafenib also interacts with the downstream signalling cascade by inhibiting the serine-threonine Raf-1 kinase [2, 9–11]. The majority of renal cell carcinomas overexpress the EGF receptor and/or the receptor tyrosine kinase ErbB2 (Her2). Both receptor tyrosine kinases may be inhibited by lapatinib [9, 12].

At present, of all targeted therapies, the greatest body of evidence is probably available supporting the clinical

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Fig. 1. The von Hippel-Lindau pathway in renal cell carcinoma. Non-functioning von Hippel-Lindau gene product (VHL protein, hatched) results in decreased binding and cleavage of hypoxia-inducible factor alpha (HIF-α), subsequent transfer of HIF-α into the nucleus, and binding to HIF-β, leading to the transcription of the growth factors vascular endothelial growth factor (VEGF) and platelet-derived growth factor (PDGF). The secreted growth factors bind to their receptors (vascular endothelial growth factor receptor, VEGFR, and platelet-derived growth factor receptor, PDGFR) in an autocrine and paracrine manner, causing dimerization and autophosphorylation of the transmembrane receptor protein kinases and activation of downstream signalling pathways (flashes), causing tumour cell and vascular endothelial and stromal proliferation. Data derived from Patel et al. [2] and Rini and Small [8].
use of sunitinib in metastatic renal cell carcinoma. Sunitinib as a second-line treatment after failure of cytokine-based first-line therapy produced a high rate of partial remissions [13]. In a randomized trial comparing sunitinib with interferon alpha as first-line treatments for metastatic renal cell carcinoma [14], the median progression-free survival was significantly longer in patients receiving sunitinib than in those receiving interferon alpha (11 vs. 5 months). The response rate was higher in the sunitinib group than in the interferon alpha group (31 vs. 6%, p < 0.001). There was a trend towards an increased overall survival in the sunitinib arm; the significance level set for the interim analysis was, however, not reached [14]. An example for a partial remission seen during first-line treatment with sunitinib is shown in figure 2.

For sorafenib, mature data from randomized trials are not yet available for the first-line setting. Data from a second-line trial performed in patients progressing during initial systemic treatment [15], however, indicate that this substance has also a promising activity in metastatic renal cell carcinoma. As compared with placebo, the median progression-free survival was longer in patients receiving sorafenib (5.5 vs. 2.8 months, p < 0.001), and the partial response rate was also higher with sorafenib (10 vs. 2%, p < 0.001). As with the first-line sunitinib trial [14], there was a tendency towards an improved overall survival that did not fit the required significance threshold for the interim analysis [15]. Sorafenib and sunitinib have a favourable side effect profile, with rash and diarrhoea occurring most commonly. Sorafenib treatment harbours a small risk of developing coronary heart disease and myocardial infarction which, however, seems to be outweighed by the clinical benefit of the drug [14, 15].

Bevacizumab is a monoclonal antibody binding and inactivating VEGF, thus potentially developing anti-angiogenic and antitumour activities in renal cell carcinoma. This agent was the first molecular therapy showing clinical activity in metastatic renal cell carcinoma in a randomized trial [16]. As compared with placebo, high-dose bevacizumab (10 mg/kg every 2 weeks) significantly delayed progression in patients with metastatic clear cell renal cell carcinoma with progression during prior cytokine treatment or contra-indications to such treatment. There was, however, no effect on survival [16].

Blockage of the mTOR serine-threonine protein kinase (as a part of downstream signalling pathways) is another promising molecular treatment in metastatic renal cell carcinoma. In a phase 3 trial [17], 626 patients with high-risk metastatic renal cell carcinoma were randomized into three arms: interferon alpha (up to 18 million U s.c. three times a week) versus the mTOR inhibitor temsirolimus (25 mg i.v. once a week) versus temsirolimus (15 mg i.v. once a week) plus interferon alpha (6 million U s.c. three times a week). The median survival was significantly longer in the 25-mg temsirolimus arm as compared with the interferon alpha arm (10.9 vs. 7.3 months, p = 0.0069), whereas the lower dose combined with interferon alpha was less effective (median survival 8.4 months, not significantly different from the interferon alpha arm). The toxicity profile was acceptable and was not appreciably different in the treatment arms [17].
Lapatinib has been tested as a second-line treatment in a randomized phase 3 trial in 417 patients with metastatic renal cell carcinoma - 94% had received cytokine therapy, lapatinib dose 1,250 mg daily; control arm: hormonal treatment [12]. Whereas there was no detectable overall survival difference in the whole study population (median 46.9 weeks for lapatinib vs. 43.1 weeks for hormonal treatment, p = 0.29), the overall survival was significantly improved by lapatinib treatment in the subgroup (56%) of the patients whose tumour overexpressed EGFR receptor proven by immunohistochemistry (median 46.0 weeks for lapatinib vs. 37.9 weeks for hormonal treatment, p = 0.02). The patients with EGFR receptor-overexpressing tumours apparently had a particularly poor survival when treated with hormonal therapy; this survival disadvantage seemed to be compensated by application of lapatinib. The toxicity was moderate with rash and diarrhoea, each affecting about 40% of the patients receiving lapatinib [12].

Although many molecular treatments have shown single-agent activity in renal cell carcinoma, complete remissions are extremely rare, and all patients are deemed to eventually progress and succumb to their malignancy. To improve response rates and survival or even to cure some patients, the combination of different molecular interventions is a tantalizing strategy. Molecular agents may be combined as ‘horizontal blockade’ in the case of simultaneous inhibition of different receptors (for instance VEGF and PDGF receptors by sunitinib or sorafenib plus EGFR receptor by erlotinib or lapatinib) or as ‘vertical blockade’ by intervention at more than one level in the same pathway (for instance bevacizumab plus sorafenib or lapatinib plus temsirolimus). However, such interventions harbour the risk of surprising and significant toxicity and require careful investigations in controlled trials. There are first promising results from combined treatment approaches available. Partial responses were observed by combined sorafenib and bevacizumab treatment even in patients with the sarcomatoid variant of renal cell carcinoma which is a highly aggressive subtype with a particularly poor prognosis [18]. The observed toxic effects were, however, considerable [19].

There is no consensus on the necessity of nephrectomy prior to molecularly targeted therapy for metastatic renal cell carcinomas. Most patients in randomized trials demonstrating efficacy of targeted therapy for renal cell carcinoma underwent nephrectomy initially. There is, however, still no evidence that nephrectomy improves the survival in this setting, as it did in patients subsequently receiving cytokines [20].

Docetaxel-based chemotherapy is an active treatment in patients with hormone-refractory prostate cancer. It has been shown to improve the median survival by approximately 2 months as compared with treatment with mitoxantrone plus prednisolone [21]. Two substances tested combined with docetaxel-based chemotherapy showed promising results in this setting. Although the precise mechanism of action of thalidomide is still unknown [4], it may be regarded as a ‘targeted’ cancer treatment because of its anti-angiogenic and immunomodulatory properties. In a small randomized trial comparing weekly docetaxel (30 mg/m² for 3 weeks of a 4-week cycle) with or without thalidomide (200 mg daily) [22, 23], the median survival was better in the thalidomide group (25.9 vs. 14.7 months, p = 0.04). This surprisingly high survival advantage contrasts favourably with the 2-month median survival gained by docetaxel treatment as compared with mitoxantrone plus prednisolone and calls for further evaluation of this regimen in patients with hormone-refractory prostate cancer.

The calcitriol receptor is another target with promising clinical potential in prostate cancer. Experimental in vitro and in vivo models suggest that calcitriol may induce apoptosis and inhibit tumour growth and metastatic spread [24]. In an interim analysis of a double-blind randomized trial comparing high-dose calcitriol with placebo in combination with weekly docetaxel (36 mg/m² for 3 weeks of a 4-week cycle) [25], patients receiving calcitriol had an improved overall survival. The difference just reached significance level in multivariate analysis (p = 0.035), but missed it narrowly in univariate analysis (p = 0.07). There was only a marginal difference in prostate-specific antigen response rates. High-dose calcitriol had a favourable safety profile [25].

Endothelin-1 is secreted by prostate cancer cells and promotes tumour growth and metastatic spread by autocrine and/or paracrine activity. It has been found to stimulate the mitotic activity in osteoblasts and to decrease osteoclastic bone resorption and osteoclast motility, thus promoting the development of osteoblastic bone metastases [26]. Besides some symptomatic improvement and biochemical responses of prostate-specific antigen and bone turnover markers, however, the clinical benefit of single-agent treatment with the endothelin-1 antagonist atrasentan is limited. In a meta-analysis of more than 1,000 patients with hormone-refractory prostate cancer [27], there was only a marginal difference from placebo concerning disease progression. A possible role of atrasen-
ten as a part of a combination treatment, particularly in patients with bone involvement, needs further evaluation in controlled trials. Based on the available clinical data, approval for atrasentan was not granted by the Food and Drug Administration [26].

Up to now, clinical trials investigating tyrosine kinase inhibitors or monoclonal antibodies as monotherapy for hormone-refractory prostate cancer yielded uniformly disappointing results [28–31].

**Bladder Cancer**

The molecular pathways involved in carcinogenesis and progression of invasive bladder cancer are increasingly well understood. There are several exciting options to intervene in these pathways in preclinical and clinical testing [32]. Up to now, however, there are still only a few reports on clinically meaningful benefits of molecular treatment in bladder cancer. Invasive bladder cancer cells express the receptor tyrosine kinases EGF and Her2 (fig. 3). Inhibition solely of the EGF receptor with gefitinib was without appreciable additional effect in combination chemotherapy with gemcitabine-cisplatin [33]. Lapatinib inhibits both EGF and Her2 receptor tyrosine kinases and has shown promising activity in advanced breast cancer [34]. In one study [35], patients with advanced urothelial carcinoma and immunohistochemical evidence of either EGF receptor and/or Her2 receptor overexpression who progressed after cisplatin-based first-line chemotherapy received 1,250 mg lapatinib daily as monotherapy. There were no complete and only one (although marked) partial remission by independent radiological review. However, patients with strong expression of one or both markers seemed to benefit from the treatment in terms of stabilization of the disease. The toxicity was mild, with diarrhoea and rash representing the most common side effects [35].

**Testicular Cancer**

Although a majority of seminomas and a subset of non-seminomas express c-kit [36], identifying them as potential candidates for imatinib treatment, there are no published reports on successful imatinib application in refractory germ cell tumours up to now. Among 6 patients with incurable chemotherapy-refractory germ cell tumours with c-kit expression (no difference between seminomas and non-seminomas was made), only 1 patient experienced transient stabilization of disease and tumour marker decrease [37]. A minority of refractory germ cell tumours overexpress Her2 [38]. In one case of a cisplatin-refractory germ cell tumour with Her2 expression, treatment with the monoclonal antibody trastuzumab resulted in disease remission [39]. Leydig cell tumours rarely cause metastatic disease that, however, is largely resistant to conventional treatment with chemotherapy or radiotherapy. Since Leydig cell tumours express PDGF, kit ligand, and their receptors, PDGF receptor and c-kit, they are potential candidates for imatinib.
treatment. Studies in cell lines and animal models were promising [40]. Experimental treatment in a 76-year-old man with metastatic Leydig cell tumour was, however, without detectable effect [41].

**Other Urologic Malignancies**

Due to the low frequency of other types of urologic cancers, there are only very sparse data on potentially beneficial molecular treatment strategies. In one study [42], a dramatic clinical improvement has been achieved by a combination of imatinib and thalidomide in a patient with chemotherapy-refractory recurrent undifferentiated prostate sarcoma. Adrenal carcinomas might be attractive targets for molecular therapy [43]; there are, however, still no reports on clinical advances in this field.

**Conclusions**

Molecular treatment is currently changing the standards of medical treatment of advanced renal cell carcinomas, a type of cancer with very limited non-surgical treatment options. Although much less data support targeted therapy of other urologic malignancies, it is likely that new treatment options will become available in the years ahead. Besides single-agent regimens, the combination of anti-angiogenic drugs with conventional chemotherapy may be a field of possible future advances.

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**References**

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Review


