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TOPIC PAPER

Antibody therapy in renal cell carcinoma

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Abstract The treatment of metastasized renal cell carcinoma (RCC) still represents a formidable challenge, despite the development of small molecule, tyrosine kinase inhibitors (TKI) that have made a major impact on the disease. Although the percentage of patients achieving a partial response or stabilization of disease has been impressive, these effects are mostly non-durable. Additionally, drug-related side effects can be quite severe. Alternative treatment modalities might be monoclonal antibodies (mAbs). mAbs against RCC-associated antigens have been developed and have shown promise. Additionally, current efforts focus on Bevacizumab that recognizes vascular endothelial growth factor (VEGF). VEGF overexpression in RCC provides the opportunity to inhibit this proangiogenic pathway. Also with Bevacizumab, promising results have been obtained, particularly in combination with other treatment modalities. It is likely that mAbs, either as single agents or in combination with other agents, may become useful additions to the armamentarium to diagnose and treat RCC.

Keywords Monoclonal antibody · Renal · RCC · VEGF · G250 · CAIX · Therapy

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Introduction

The hypothesis by Ehrlich in early 1900s that malignant cells express unique structures that can be used to guide cytotoxic therapy to tumors [1] followed by the development of the hybridoma technique by Kohler and Milstein almost 70 years later [2] has led to the development of anticancer reagents with unique characteristics. One of the most distinguishing factors is the possibility to select monoclonal antibodies (mAbs) recognizing target molecules with very restricted expression in normal tissues. To date, tumor-specific antigens (antigens expressed on all tumor cells of a particular tumor type not expressed by normal cells) have not been identified. The members of the so-called cancer-testis family do exhibit highly tissue-restricted expression, but are considered promising target molecules for cancer vaccines, less for antibody therapy, particularly in view of the extreme intra- and inter-tumor heterogeneity [3].

Similar to other malignancies, monoclonal antibodies (mAbs) targeting renal cell carcinoma (RCC) associated molecules were developed without understanding the molecular events underlying RCC [4–8]. The increased understanding of molecular events important in the carcinogenesis of RCC led to the recognition that these aberrations can be used to target RCC. Specifically, aberrant von Hippel-Lindau (VHL) gene expression has been identified as a general event in clear cell RCC (ccRCC) [9],

which represents 80–85% of localized cases and 90–95% of metastatic RCC (mRCC). The loss of a functional VHL gene product leads to accumulation of the transcription factor HIF-1α that is an obligatory element for the transcription of several genes. This includes vascular endothelial growth factor (VEGF) and carbonic anhydrase 9 (CA9), targets for which most clinical experience with mAbs in RCC has been generated (Bevacizumab and G250, respectively).

The rationale and effects of Bevacizumab and G250-directed therapy are fundamentally different: Bevacizumab treatment leads to VEGF-depletion and consequently to diminished neovascularization followed by tumor cell death, mainly due to loss of vascularization. In contrast, G250 treatment targets the cell surface of RCC cells where it must exert toxic effects. Both approaches have advantages and disadvantages. Bevacizumab treatment has the advantage that VEGF depletion can be achieved in the circulation, and homing to all tumor vessels is not necessary. However, other regulatory pathways can also lead to neovascularization and small, non-vascularized tumor loci will not be affected. G250 treatment has the advantage that RCC cells can be targeted, irrespective of tumor size. However, in view of the generally poor perfusion rate and high interstitial fluid pressure in RCC, deep penetration of tumors may be difficult. Also, since G250-binding alone does not confer a lytic signal to RCC cells, tumor cell kill requires effector cells or coupling of G250 to toxic agents.

Bevacizumab

Bevacizumab is a humanized mAb against VEGF that binds and neutralizes all of the major isoforms of VEGF [10]. This prevents VEGF from interacting with its receptors and activation of downstream signaling pathways. This mode of action is thought to lead to regression of existing microvasculature, normalization of mature vasculature, and inhibition of the production of new vasculature [11]. Whether all these effects are true for RCC is unclear at the moment.

Significant protein dose levels are needed to maintain sufficiently high Bevacizumab levels to trap VEFG, the target of Bevacizumab. The first Bevacizumab trial in metastatic RCC (mRCC) patients addressed whether Bevacizumab treatment could lengthen the time to progression of disease and the response rate [12]. Survival was a secondary end point. In this randomized phase II trial, 116 patients with metastatic, refractory clear cell RCC were randomized to placebo, low-dose (3 mg/kg) Bevacizumab, or high-dose (10 mg/kg) Bevacizumab given intravenously every 2 weeks. All patients had prior disease progression while on systemic treatment; the vast majority had received prior interleukine-2. Patients with disease progression on placebo crossed over to receive low-dose Bevacizumab. Bevacizumab treatment resulted in a significant prolongation of the time to progression of disease in the high-dose antibody group (4.8 months as compared with 2.5 months). Possibly, the low-protein dose was inadequate to sufficiently deplete circulating VEGF levels in-between injections, explaining the poor outcome in this group. The study was inadequately powered to show a significant difference in overall survival between groups. Based on this encouraging result, Bevacizumab has been combined with other treatment modalities to augment the therapeutic index.

Bevacizumab in combination

The AVOREN trial investigated the effects of standard therapy of interferon alfa-2a plus placebo or interferon alfa-2a plus Bevacizumab, administered every 2 weeks at a dose of 10 mg/kg [13]. In this randomized, double blind phase III trial, 649 patients with first-line mRCC were enrolled. The primary analysis endpoint was assessment of improvement in progression-free survival (PFS), defined as the length of time the tumor did not grow or patient death did not occur. Other endpoints of the study included overall survival, time to progression, time to treatment failure, overall response rate, and safety profile. The addition of Bevacizumab to IFN-α2a significantly increased PFS (10.2 vs. 5.4 months) and objective tumor response rate (30.6 vs. 12.4%; $P < 0.0001$). Additionally, the combination treatment showed a trend toward improved overall survival ($P = 0.0670$), which leads to the conclusion that the combination of Bevacizumab with IFN-α2a is superior to either of the single treatment regimens in mRCC. The working mechanism explaining the superiority of this combination treatment has not been defined yet, but most likely the superiority is the net effect of the reduction of the immunosuppressive effects due to decreased VEGF levels combined with the immunomodulatory effects of IFN.

Considering that the epidermal growth factor receptor (EGFR) is also overexpressed in RCC, a multicenter, phase II study evaluated the addition of erlotinib (Tarceva), an EGFR inhibitor, to Bevacizumab in metastatic RCC patients [14]. Treatment consisted of 10 mg/kg Bevacizumab given intravenously every 2 weeks and 150 mg erlotinib given orally each day. With 15 (25%) patients showing objective responses, and an additional 36 patients (61%) with stable disease after 8 weeks of treatment, a randomized phase II trial was performed evaluating Bevacizumab + placebo versus Bevacizumab + erlotinib. Disappointingly, identical response rates and PFS rates for

the two arms were observed [15], and it is doubtful that EGFR-targeting is of any benefit.

The effect of Bevacizumab and low-dose interleukine-2 (IL-2) in mRCC was evaluated in a phase II trial in previously untreated, good and intermediate risk, mRCC patients. Patients received 8-week cycles of IL-2 (250,000 U/kg per day s.c. Day 1–5 during week 1 and 125,000 U/kg per day s.c. Day 1–5 during weeks 2–6, followed by a 2 week break), and Bevacizumab 10 mg/kg was administered i.v. every 2 weeks starting on day-14. With 16 of the planned 35 patients enrolled, and 11 evaluable patients for response, 1 partial response (PR) and 3 stable disease (SD) lasting >3 months were observed [16]. All patients with SD demonstrated some degree of tumor shrinkage. Similar to the working mechanism of the Bevacizumab/IFN combination, the anti-tumor effects are possibly the result of the reduction of the immunosuppressive effects due to decreased VEGF levels combined with the general immune activating effects of IL-2. Interestingly, treated patients demonstrated an increase in the number of regulatory T cells without effect on DC activation. Larger, randomized studies will be necessary to address the value of this combination treatment.

In a phase I trial, Bevacizumab has also been combined with sunitinib (Sutent®), a tyrosine kinase inhibitor, with the hypothesis that this combination may increase antitumor efficacy by maximizing inhibition of the VEGF pathway. The Bevacizumab dose was kept constant (10 mg/kg) while the sunitinib dose was escalated starting at 25 mg (escalation with 12.5 mg increments). Of 13 patients evaluated for best response, 4 had partial responses, 7 had stable disease, and 2 had PD [17].

Similarly, the combination of Bevacizumab and the mTOR inhibitor CCI-779 (Temsirolimus®) has been investigated. Patients received 25 mg/week Temsirolimus and 5 or 10 mg/kg Bevacizumab. In 12 evaluable patients, 7 PR and 3 SD were observed [18]. The encouraging results certainly deserve further testing of these combinations in phase II trials.

Monoclonal antibody G250

G250 is a mAb against CA9, a molecule which is ubiquitously expressed in ccRCC [19]. CA9 expression in non-ccRCC has also been documented, and there, it is most likely a reflection of (sustained) hypoxia [20]. Clinical efforts with mAb G250 in RCC have focused on radioimmunotherapy and passive immunotherapy. This mAb was described as a mAb recognizing an RCC-associated antigen, absent in normal kidney and homogeneously expressed in most RCC [4], most notably clear cell RCC [19]. In 2000, the G250 antigen molecule was identified and shown to be CA9 [21]. The molecular characterization allowed transcriptional regulation studies that revealed a strict dependence of G250 expression on HIF-1α [22]. Thus, the molecular mechanism responsible for CAIX expression in ccRCC is similar to VEGF, namely due to non-functional VHL protein leading to HIF-1α accumulation and gene expression.

The first clinical trials with mAbG250 were already performed and published before the molecular characterization of G250 antigen was achieved. The combined data from the immunohistochemical tissue distribution, animal experiments and ex vivo perfusion of tumor bearing kidneys had provided sufficient evidence to initiate a biopsy-based phase I protein dose escalation trial with murine mAbG250. The rationale of G250-directed therapy obviously differs from Bevacizumab: Bevacizumab treatment leads to VEGF-depletion and consequently to diminished neovascularization whereas G250 treatment targets RCC cells directly. This first mAbG250 clinical trial demonstrated various pivotal aspects: most notably, virtually no uptake in other tissues resulting in excellent tumor visualization, and very high tumor uptake [23].

The G250 antibody uptake that was observed was up to 10-fold higher than any other mAb uptake in solid tumors, which led to the design of a phase I/II radioimmunotherapy (RIT) trial with murine mAbG250. RIT led to stabilization of disease in 17 of 33 patients, with tumor shrinkage observed in two patients. Transient liver toxicity was observed, quite likely the result of mAbG250 liver uptake, although there was no correlation between the amount of ^{131}I administered or hepatic absorbed radiation dose and the extent and nature of hepatic toxicity [24].

Because the murine G250 antibody was highly immunogenic, restricting multiple injections, mAbG250 was chimerized. The results of the phase I protein dose escalation trial with chimeric G250 (cG250) basically duplicated the results from the murine G250 trial: virtually no uptake in other tissues resulting in excellent tumor visualization, and very high tumor uptake. The half-life of the antibody was extended, as was to be expected, but, more importantly, the chimerized from of G250 was almost immunosilent [25]. Thus, multiple injections became possible. Various phase I and phase II trials have been performed with cG250 aimed at therapeutic intervention. Based on the very high uptake levels, several RIT trials were performed. In the first phase I trial with ^{131}I-cG250, one patient showed a partial response (>9 months) [26] which set the stage for phase II RIT trials in metastatic RCC patients. RIT studies with single high dose ^{131}I-G250, rapid fractionated dose ^{131}I-G250 [27], and sequential high dose ^{131}I-G250 [28] have resulted in only occasional therapeutic responses, although dosimetric analyses suggest that tumor-sterilizing levels can be reached. Even two

sequential high-dose treatments with ^{131}I-G250 did not result in objective responses, but in stabilization of previously progressive disease in a few patients. RIT with G250 has been accompanied by bone marrow toxicity similar to mAb RIT in other tumor types and considering the minimal benefit, ^{131}I-based RIT with cG250 have been abandoned. Since RCC is a radiotherapy resistant tumor, possibly even higher radiation doses are necessary to achieve tumor-sterilizing levels. Current G250 RIT efforts are directed to 177-lutetium and 90-yttrium labeled G250. It is hypothesized that the use of more powerful radionuclides that are also better retained in the tumor cells may lead to clinical responses. Animal experiments have demonstrated the superiority of ^{177}Lu- and ^{90}Y-labeled G250 over ^{131}I-G250 [29]. Importantly, stabilization of previously progressive disease has been observed in almost all ^{177}Lu-G250 treated patients, although the maximum tolerable ^{177}Lu dose has not been achieved. Dosimetric analyses of the first patients treated with ^{177}Lu-G250 suggest that indeed tumor-sterilizing levels may be achieved. Figure 1 illustrates targeting of ^{177}Lu-G250 in a patient with metastatic renal cancer.

In view of the obvious tumor-specific accumulation of cG250, passive immunotherapy of RCC patients has also been studied extensively. In vitro mAbG250 can elicit antibody-dependent cellular cytotoxicity (ADCC), which can be enhanced by low dose IL-2 [30]. Various (non-randomized) clinical trials have now been completed with cG250 alone, and in combination with IL2 or interferon [31, 32]. Thus far, these treatments appear to lead to extended survival time. The apparent clinical benefit appears to be quite substantial with a documented median survival of 22 months in patients with metastatic RCC who have progressive disease at study entry. Nevertheless, it is difficult to judge the value of this treatment. Clearly, randomized trials are necessary to unequivocally demonstrate whether passive immunotherapy with cG250 is of benefit for metastatic RCC patients.

The largest trial, which is currently ongoing, is the adjuvant ARISER trial (adjuvant Rencarex immunotherapy phase III trial to study efficacy in nonmetastatic renal cell carcinoma). In this phase III randomized, double blind, placebo-controlled trial, patients with ECOG performance status of 0 with completely resected primary clear cell RCC and no evidence of remaining local or distant disease, are treated. The study is designed to detect a significant difference between the two treatment arms with respect to disease-free survival; patients will be followed-up long-term to determine overall survival statistics.

Recently, the potential utility of mAbG250 as a diagnostic imaging agent was investigated [33]. The excellent imaging capability had been noted in almost all patients, but this line of research was not pursued mainly because detection of suspect renal masses and occult metastatic

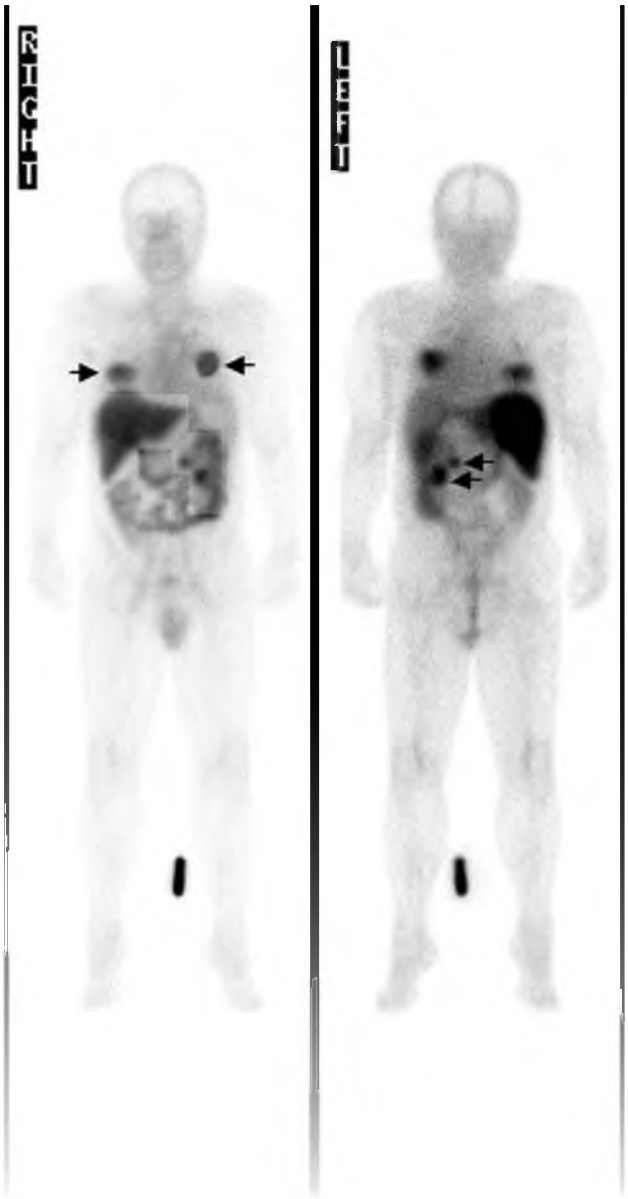

Fig. 1 Anterior (*left*) and posterior (*right*) whole body scans acquired 7 days post-injection of patient injected with^{177}Lu-cG250. Please note high uptake in both pulmonary lesions and in contralateral kidney lesions. Uptake in liver is due to the conjugation methodology and is not related to G250 antigen expression

RCC was not deemed advantageous. Additionally, treatment modalities for metastasized RCC were poor, and, therefore, efforts focused on treatment. However, with a steady increase of incidentally discovered renal masses and new therapeutic modalities becoming available, imaging might become of importance to distinguish more potentially malignant tumours from less aggressive variants. In the first prospective clinical trial with ^{124}I-labeled cG250, a very high specificity and sensitivity to identify ccRCC in patients with suspect renal masses was demonstrated, a clear indication of the potential clinical utility. Whether

this imaging modality can be used to follow therapy effects remains to be determined.

In conclusion, it is reasonable to assume that Bevacizumab and G250 monoclonal antibodies either as single agents or in combination with other agents may become useful additions to the armamentarium to diagnose and treat (cc)RCC. Several trials evaluating the combination of G250 or Bevacizumab with registered RCC treatments are currently in progress and will further define the role of these mAbs in RCC.

Conflict of interest statement There is no conflict of interest.

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